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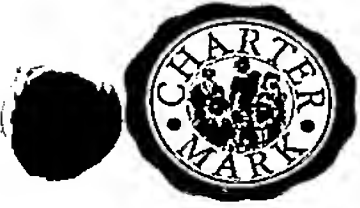
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47627.GB06/NT

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0420615.7

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Cambridge Biotechnology Ltd
 P.O. Box 230
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 United Kingdom

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of incorporation

08208761002
 United Kingdom

4. Title of the invention

Therapeutic Compounds

5. Full name, address and postcode in the United Kingdom to which all correspondence relating to this form and translation should be sent

Reddie & Grose
 16 Theobalds Road
 LONDON
 WC1X 8PL

Patents ADP number (if you know it)

91001 ✓

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Country

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Number of earlier application

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Patents Form 1/77

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11. Do we request the grant of a patent on the basis of this application.

Signature(s) *Reddie & Grose*

Date 16 September 2004

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01223 360 350**Warning**

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DUPLICATE

47627.GB06

Therapeutic Compounds

This invention relates to compounds that are adenosine receptor agonists, and to their use as therapeutic compounds, in particular as analgesic or anti-inflammatory compounds, or as disease-modifying antirheumatic drugs (DMARDs), and to methods of preventing, treating, or ameliorating pain or inflammation using these compounds.

Adenosine is a ubiquitous local hormone/neurotransmitter that acts on four known receptors, the adenosine A1, A2A, A2B and A3 receptors. Adenosine generally serves to balance the supply and demand of energy in tissues. For example, in the heart released adenosine slows the heart by an A1 receptor mediated action in the nodes and atria (Belardinelli, L & Isenberg, G Am. J. Physiol. 224, H734-H737), while simultaneously dilating the coronary artery to increase energy (i.e. glucose, fat and oxygen) supply (Knabb et al., Circ. Res. (1983) 53, 33-41). Similarly, during inflammation adenosine serves to inhibit inflammatory activity, while in conditions of excessive nerve activity (e.g. epilepsy) adenosine inhibits nerve firing (Klitgaard et al., Eur J. Pharmacol. (1993) 242, 221-228). This system, or a variant on it, is present in all tissues.

Adenosine itself can be used to diagnose and treat supraventricular tachycardia. Adenosine A1 receptor agonists are known to act as powerful analgesics (Sawynok, J. Eur J Pharmacol. (1998) 347, 1-11). Adenosine A2A receptor agonists are known to act as anti-inflammatory agents (for example, from US 5,877,180 and WO 99/34804). In experimental animals, A2A receptor agonists have been shown to be effective against a wide variety of conditions including sepsis, arthritis, and ischaemia/reperfusion injury arising from renal, coronary or cerebral artery occlusion. The common factor in these conditions is a reduction in the inflammatory response caused by the inhibitory effect of this receptor on most, if not all, inflammatory cells.

However, the ubiquitous distribution of adenosine receptors means that administration of adenosine receptor agonists causes adverse side effects. This has generally precluded the development of adenosine-based therapies. Selective A1 receptor agonists cause bradycardia. A2A receptor agonists cause widespread vasodilation

with consequent hypotension and tachycardia. The first selective A2A receptor agonist (2-[4-(2-carboxyethyl)phenylethylamino]-5'-N-ethylcarboxamidoadenosine, or CGS21680), was tested in a Phase 2A clinical trial as a potential anti-hypertensive. However, administration caused a large fall in blood pressure and consequent increase in cardiac output. FR 2162128 discloses that adenosine derivatives (including 2-alkoxy adenosine derivatives comprising a lower alkyl group of not less than two carbon atoms) have hypotensive and coronary vasodilatory activity.

Spongiosine was first isolated from the tropical marine sponge, *Cryptotethia crypta* in 1945 (Bergmann and Feeney, J. Org. Chem. (1951) 16, 981, Ibid (1956) 21, 226), and was the first methoxypurine found in nature. It is also known as 2-methoxyadenosine, or 9H-purin-6-amine, 9- α -D-arabinofuranosyl-2-methoxy. The first biological activities of spongiosine were described by Bartlett *et al.* (J. Med. Chem. (1981) 24, 947-954). Spongiosine (and other compounds) was tested for its skeletal muscle-relaxant, hypothermic, cardiovascular and anti-inflammatory effects in rodents following oral administration (anti-inflammatory activity was assessed by inhibition of carageenan-induced oedema in a rat paw). Spongiosine caused 25% inhibition of carageenan-induced inflammation in rats at 20 mg/kg po. However, reductions in mean blood pressure (41%), and in heart rate (25%) were also observed after administration of this compound at this dose.

The affinity of spongiosine for the rat adenosine A1 and A2A receptors has been determined. The Kd values obtained (in the rat) were 340nM for the A1 receptor and 1.4 μ M for the A2A receptor, while the EC50 value for stimulation of the rat A2A receptor was shown to be 3 μ M (Daly *et al.*, Pharmacol. (1993) 46, 91-100). In the guinea pig, the efficacy of spongiosine was tested in the isolated heart preparation and the EC50 values obtained were 10 μ M and 0.7 μ M for the adenosine A1 and A2A receptors, respectively (Ueda *et al* J Med Chem (1991) 34, 1334-1339). Because of the low potency and poor receptor selectivity of this compound it was largely ignored in favour of more potent and receptor selective adenosine receptor agonists.

Pain has two components, each involving activation of sensory neurons. The first component is the early or immediate phase when a sensory neuron is stimulated, for

instance as the result of heat or pressure on the skin. The second component is the consequence of an increased sensitivity of the sensory mechanisms innervating tissue which has been previously damaged. This second component is referred to as hyperalgesia, and is involved in all forms of chronic pain arising from tissue damage, but not in the early or immediate phase of pain perception.

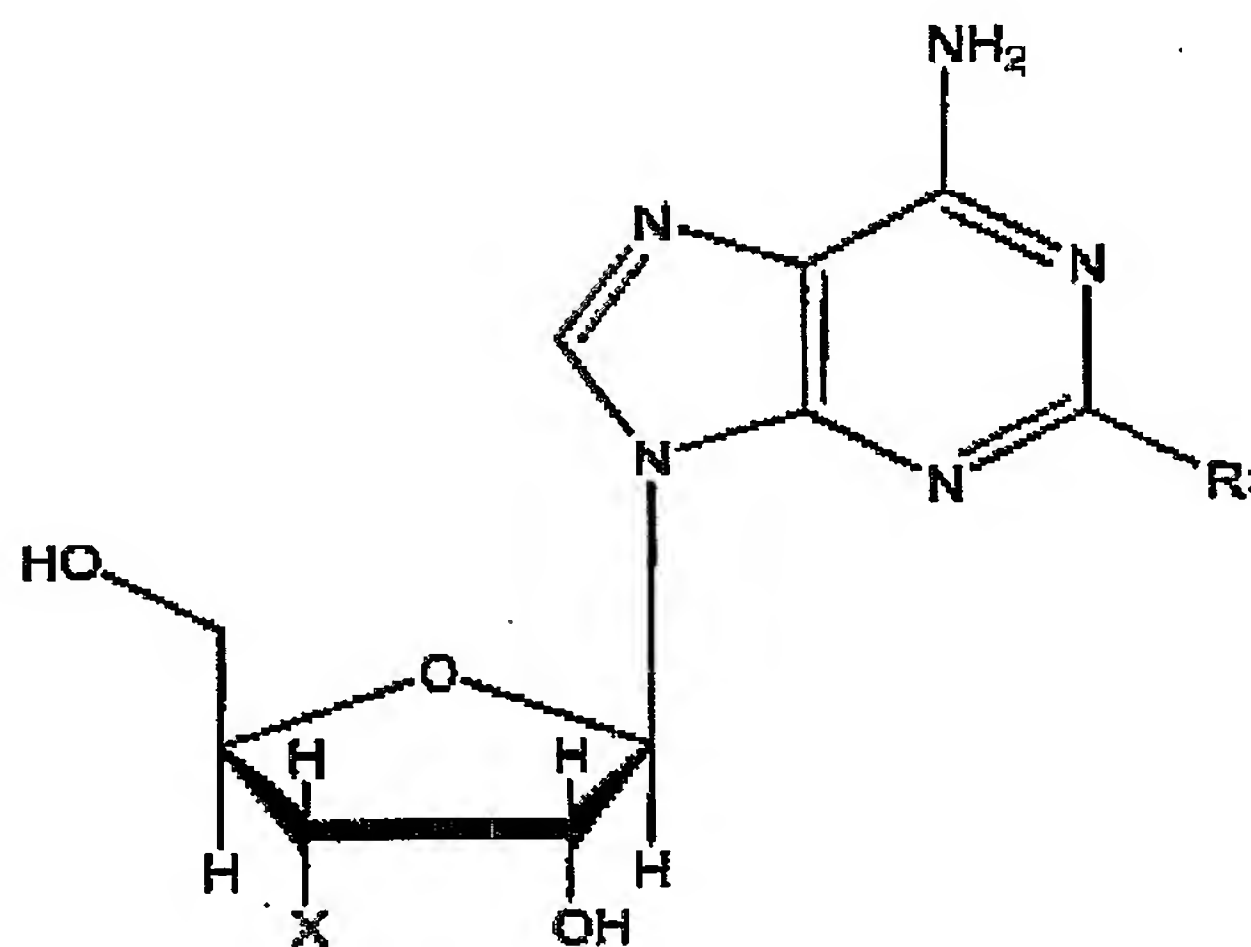
Thus, hyperalgesia is a condition of heightened pain perception caused by tissue damage. This condition is a natural response of the nervous system apparently designed to encourage protection of the damaged tissue by an injured individual, to give time for tissue repair to occur. There are two known underlying causes of this condition, an increase in sensory neuron activity, and a change in neuronal processing of nociceptive information which occurs in the spinal cord. Hyperalgesia can be debilitating in conditions of chronic inflammation (e.g. rheumatoid arthritis), and when sensory nerve damage has occurred (i.e. neuropathic pain).

Two major classes of analgesics are known: (i) non steroidal anti-inflammatory drugs (NSAIDs) and the related COX-2 inhibitors; and (ii) opiates based on morphine. Analgesics of both classes are effective in controlling normal, immediate or nociceptive pain. However, they are less effective against some types of hyperalgesic pain, such as neuropathic pain. Many medical practitioners are reluctant to prescribe opiates at the high doses required to affect neuropathic pain because of the side effects caused by administration of these compounds (such as restlessness, nausea, and vomiting), and the possibility that patients may become addicted to them. NSAIDs are much less potent than opiates, so even higher doses of these compounds are required. However, this is undesirable because these compounds cause irritation of the gastrointestinal tract.

There is, therefore, a need to provide adenosine receptor agonists that can be administered with minimal side effects. There is also a need to provide analgesics, particularly anti-hyperalgesics, which are sufficiently potent to control pain perception in neuropathic and other hyperalgesic syndromes, and which do not have serious side effects or cause patients to become addicted to them.

It has surprisingly been found that spongosine is an effective analgesic at doses as much as one hundred times lower than would be expected to be required based on the known affinity of this compound for adenosine receptors. At these doses, spongosine does not cause the significant side effects associated with higher doses of this compound, or other adenosine receptor agonists. The activity of spongosine as an analgesic is the subject of International patent application no. PCT/GB03/05379, and the activity of compounds related to spongosine as analgesics is the subject of International patent application no. PCT/GB04/00935 (unpublished at the filing date of the present application). Use of spongosine and related compounds to treat inflammation and other disorders is the subject of International patent application no. PCT/GB04/000952 (unpublished at the filing date of the present application).

According to the invention there are provided adenosine receptor agonists of the following formulae:

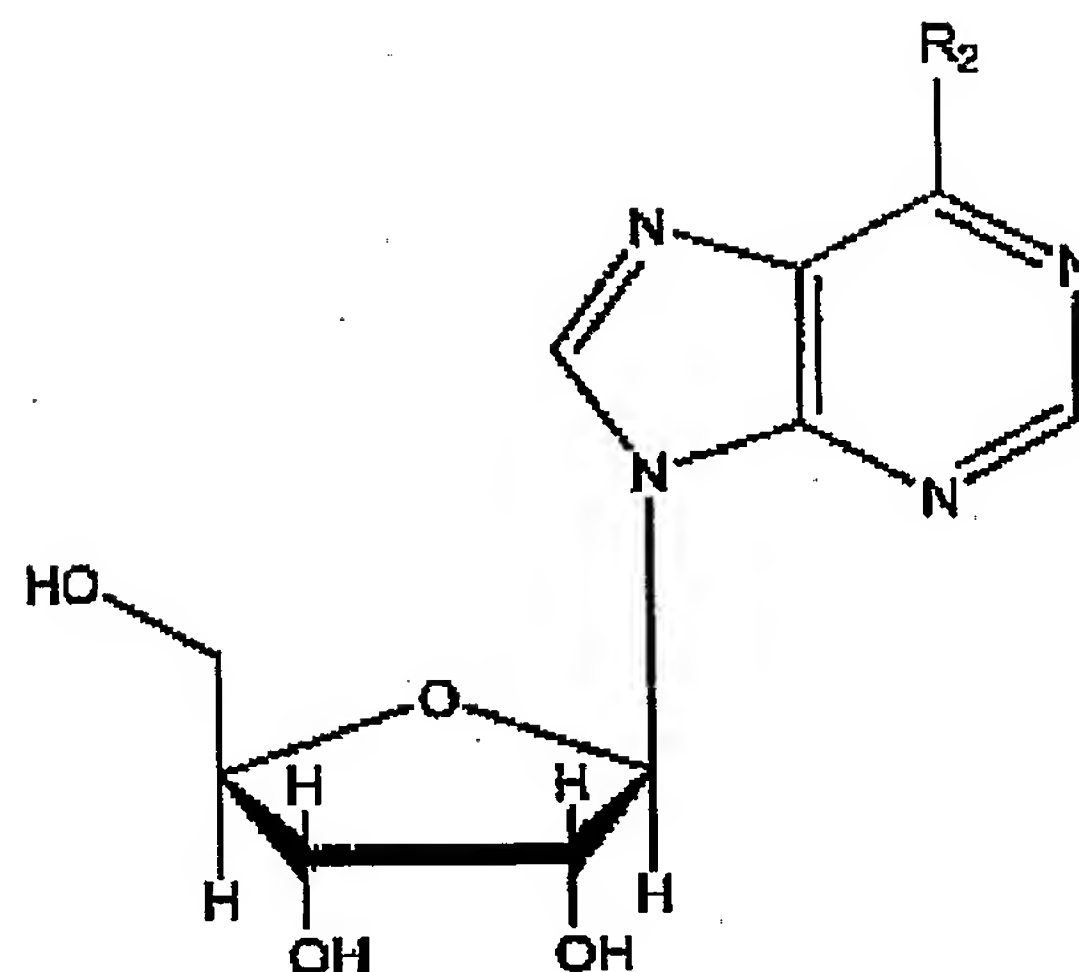


(I)

wherein:

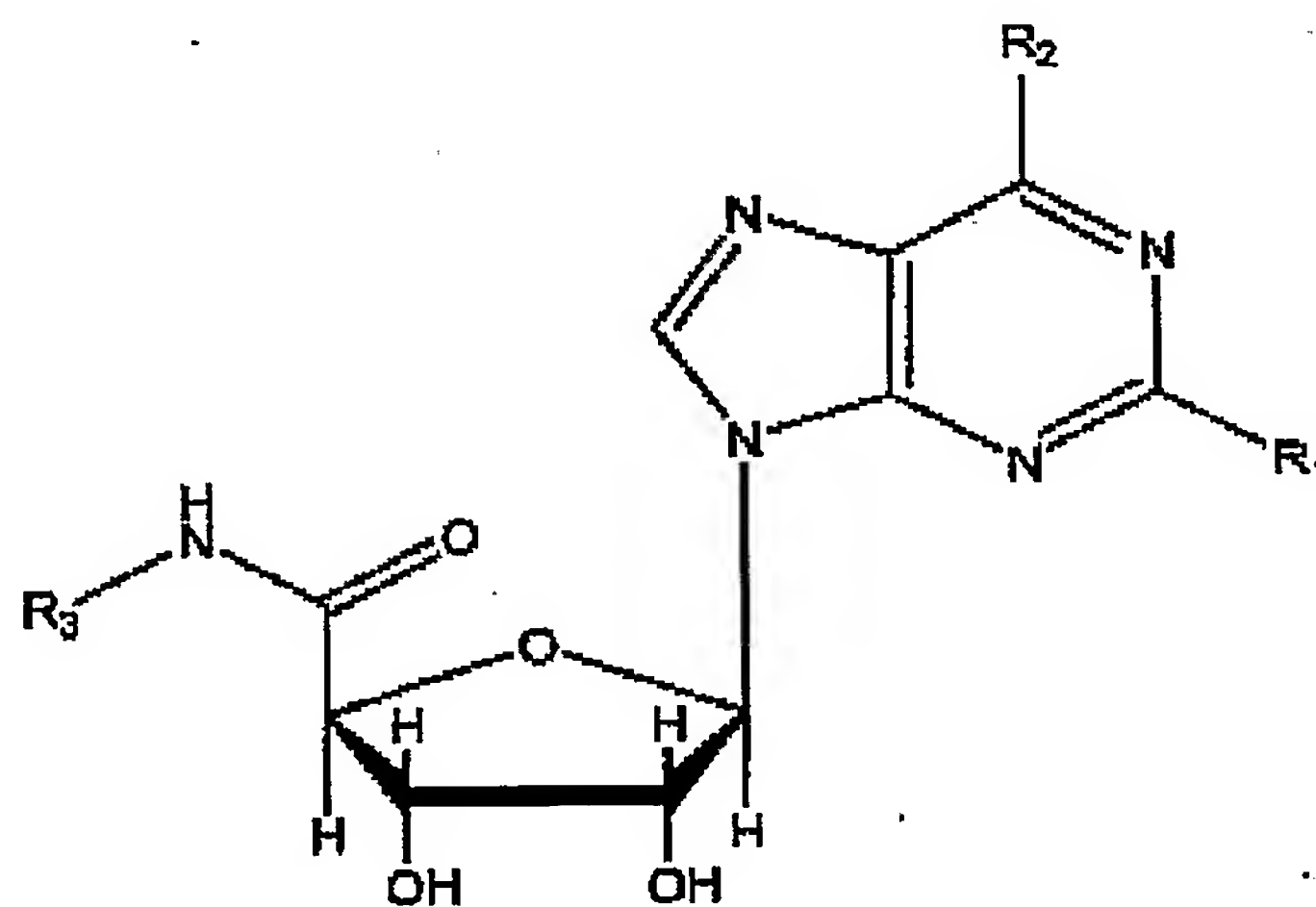
when $\text{X} = \text{OH}$, R_1 is C_1 or $\text{C}_4\text{-C}_6$ alkoxy (preferably $\text{C}_5\text{-C}_6$ alkoxy), phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1 , C_2 , C_5 , or C_6 alkylamino (straight chain or cyclic), phenylamino, phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or $\text{OCH}_2\text{CH}_2\text{OH}$; or

when $\text{X} = \text{H}$, R_1 is *n*-hexyloxy.



(II)

wherein R_2 is NMe_2 , N -(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



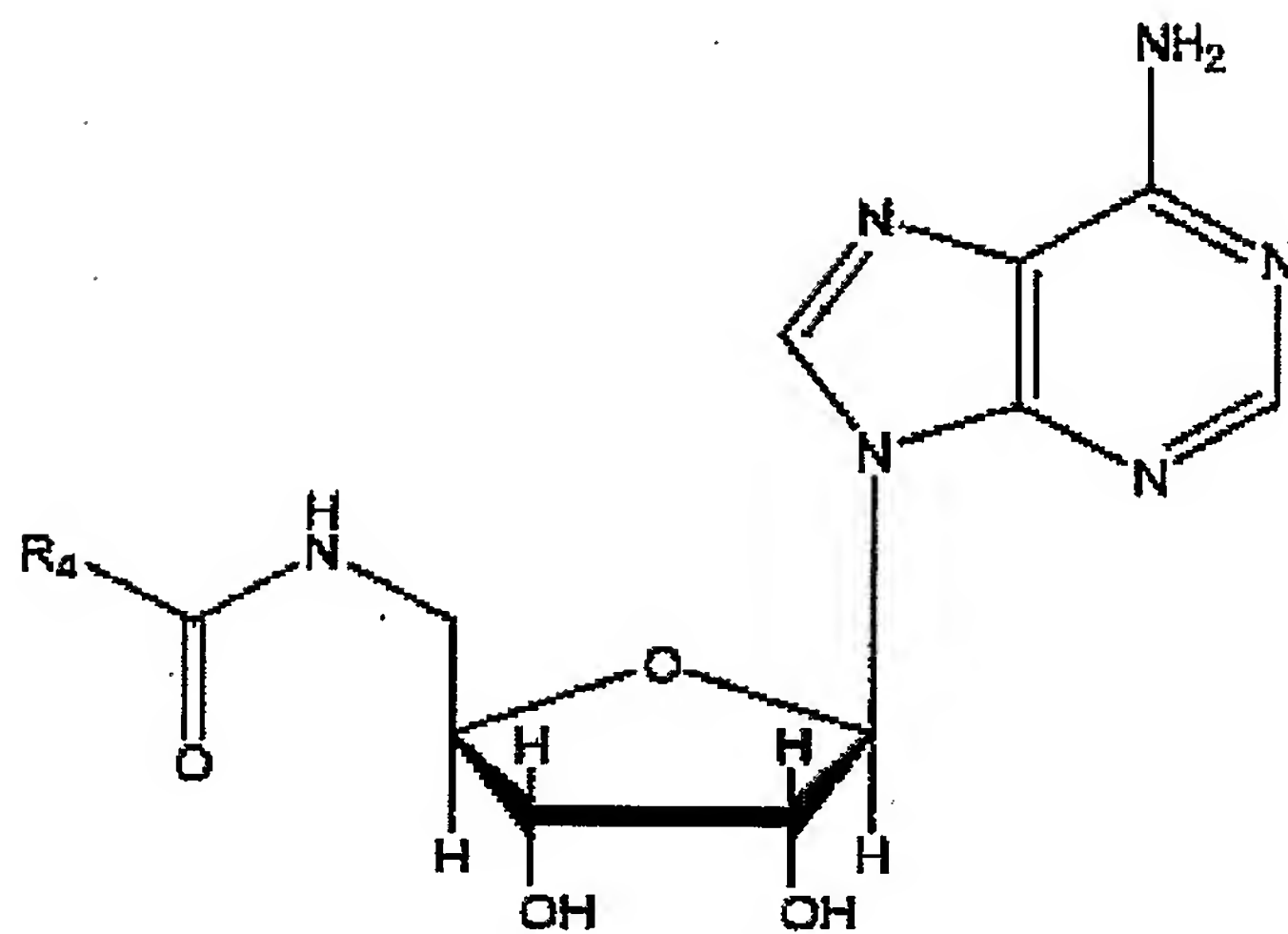
(III)

wherein:

when $R_1 = H$, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group ($NHMe$); or

when $R_1 = H$, R_3 is H , and R_2 is NH_2 ; or

when R_1 is OMe , R_3 is Ph , and R_2 is NH_2 ;

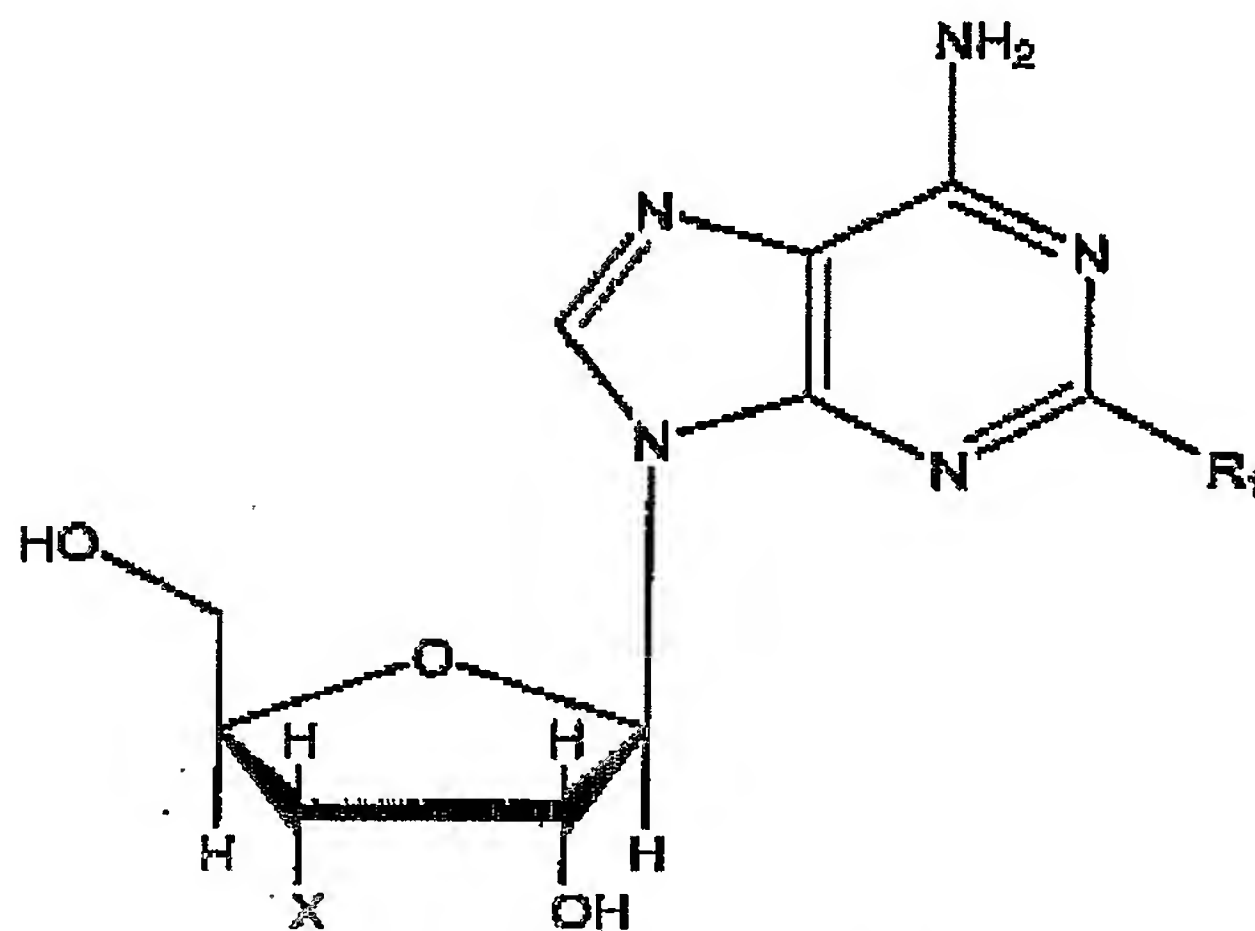


(IV)

wherein R_4 is *n*-propyl or $NHCH_2CH_3$;

or a pharmaceutically acceptable salt thereof.

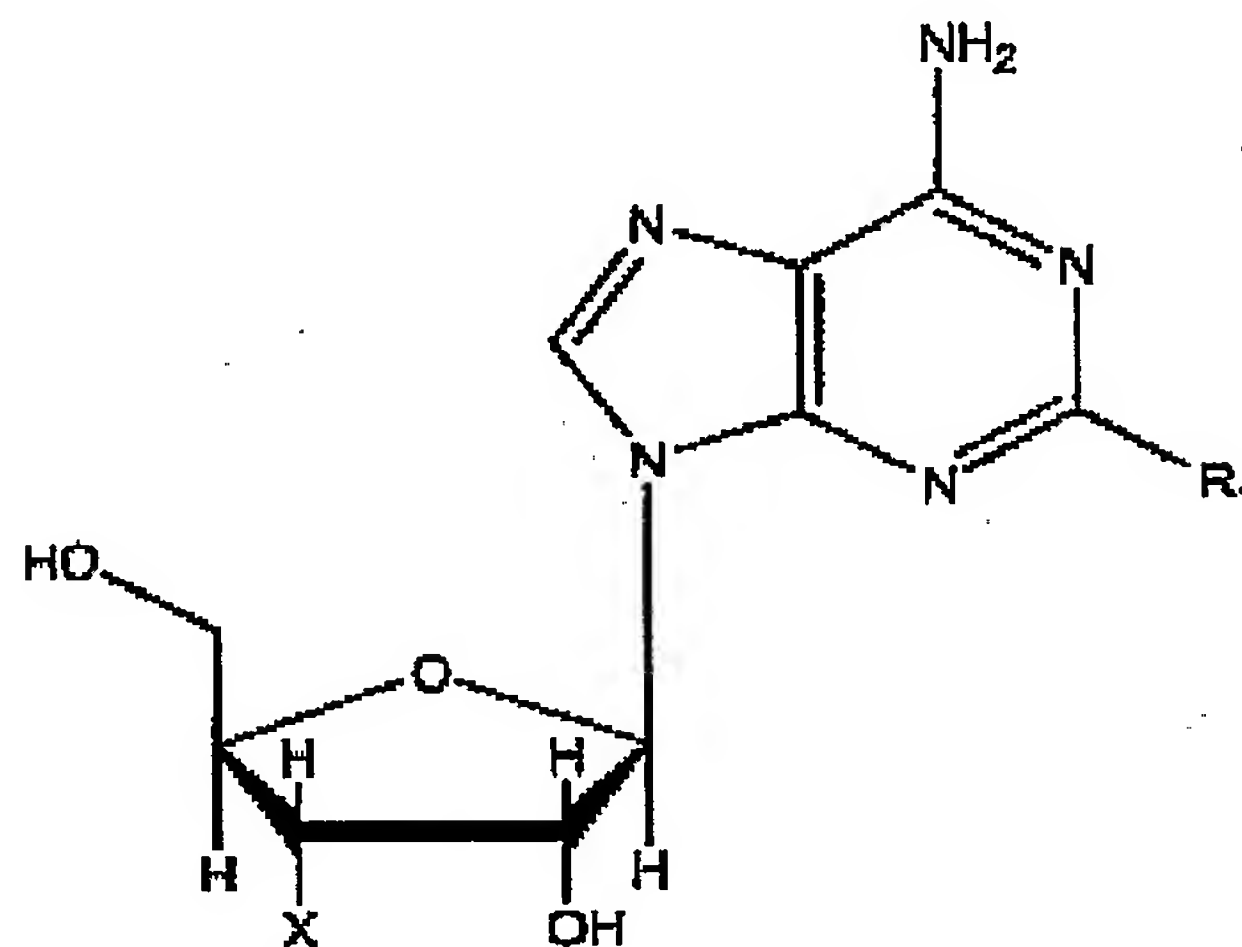
Preferred compounds of formula (I) are compounds of formula (I)(a) or (I)(b):



(I)(a)

wherein:

when $X = OH$, R_1 is C_5 - C_6 alkoxy, phenoxy substituted with nitrile, phenyl or 3-isopropyl, (5-indanyl)oxy, C_5 or C_6 alkylamino, (N-methyl, N-isoamylamino), a C_2 sulfone group, or a C_7 alkyl group; or
when $X = H$, R_1 is *n*-hexyloxy;
or a pharmaceutically acceptable salt thereof;



(I)(b)

wherein:

when $X = OH$, R_1 is phenoxy, substituted phenoxy, C_1 or C_2 alkylamino, phenylamino with either methoxy or fluoro substituents, or OCH_2CH_2OH ; or
when $X = H$, R_1 is *n*-hexyloxy;
or a pharmaceutically acceptable salt thereof.

There is also provided according to the invention a compound of the invention for use as a medicament.

It is believed that compounds of formulae (I)-(IV) have analgesic and/or anti-inflammatory activity and can be administered with reduced probability and severity of side effects compared to other adenosine receptor agonists.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, particularly hyperalgesia.

There is also provided according to the invention a method of preventing, treating, or ameliorating pain (particularly hyperalgesia) which comprises administering a compound of formula (I), (II), (III), or (IV) to a subject in need of such prevention, treatment, or amelioration.

Preferred compounds of formula (I), (II), (III), and (IV) are detailed in the Examples.

Compounds of formulae (I)-(IV) are believed to be effective in inhibiting pain perception in mammals suffering from pain, in particular neuropathic or inflammatory pain, even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. Therefore, it is believed that compounds of formulae (I)-(IV) can treat pain (particularly neuropathic and inflammatory pain) without causing the significant side effects associated with administration of other adenosine receptor agonists.

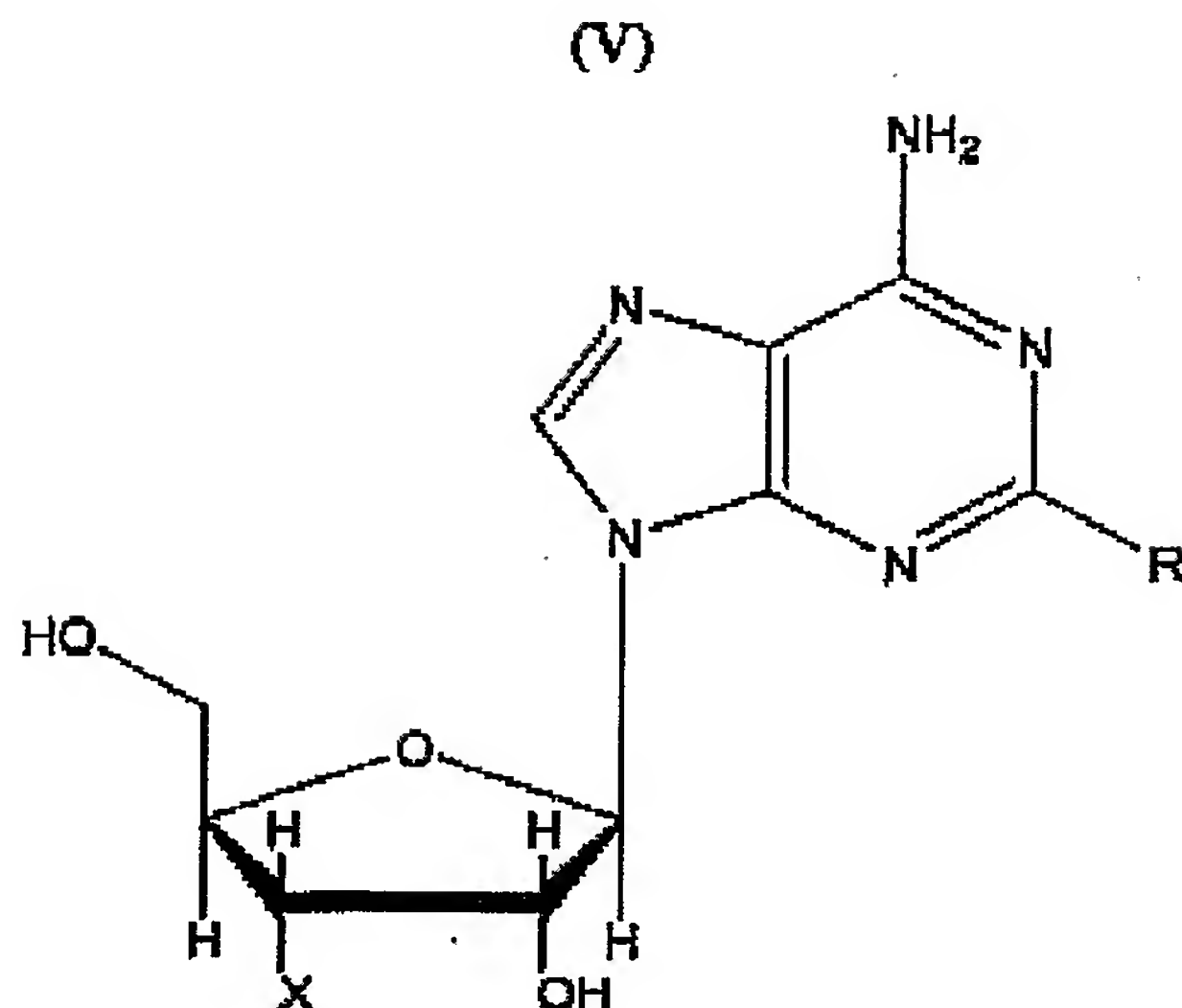
As mentioned above hyperalgesia is a consequence in most instances of tissue damage, either damage directly to a sensory nerve, or damage of the tissue innervated by a given sensory nerve. Consequently, there are many conditions in which pain perception includes a component of hyperalgesia.

According to the invention there is provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of neuropathy, including Diabetic Neuropathy, Polyneuropathy, Cancer Pain, Fibromyalgia, Myofascial Pain Syndrome, Osteoarthritis, Pancreatic Pain, Pelvic/Perineal pain, Post Herpetic Neuralgia, Rheumatoid Arthritis, Sciatica/Lumbar Radiculopathy, Spinal Stenosis, Temporo-mandibular Joint Disorder, HIV pain, Trigeminal Neuralgia, Chronic Neuropathic Pain, Lower Back Pain, Failed Back Surgery pain, back pain, post-operative pain, post physical trauma pain (including gunshot, road traffic accident, burns), Cardiac pain, Chest pain, Pelvic pain/PID, Joint pain (tendonitis, bursitis, acute arthritis), Neck Pain, Bowel Pain, Phantom Limb Pain, Obstetric Pain (labour/C-Section), Renal Colic, Acute Herpes Zoster Pain, Acute Pancreatitis Breakthrough Pain (Cancer), Dysmenorrhoea/Endometriosis.

According to the invention there is also provided use of a compound of formula (I), (II), (III), or (IV) as an analgesic (particularly an anti-hyperalgesic) for the prevention, treatment, or amelioration of pain (particularly hyperalgesia) caused as a result of inflammatory disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage, including rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, and other arthritic conditions, cancer, HIV, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury (including damage caused to organs as a consequence of reperfusion following ischaemic episodes e.g. myocardial infarcts, strokes), autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis) graft v. host rejection, allograft rejections, fever and myalgia due to infection, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis, bowel pain, cancer pain, back pain, fibromyalgia, post-operative pain.

It has also been appreciated that spongosine may be effective in the prevention, treatment, or amelioration of ischaemic pain. It is believed that compounds related to spongosine may also be effective against ischaemic pain.

According to the invention there is provided use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of pain, in particular ischaemic pain:



wherein R is C₁₋₄ alkoxy, and X is H or OH,
or a pharmaceutically acceptable salt thereof.

Preferably R is C₁₋₄ alkoxy; and X is OH, or a pharmaceutically acceptable salt thereof. Compounds of formula (V) may exclude 2-methoxyadenosine (spongosine).

There is also provided according to the invention a method of preventing, treating, or ameliorating pain, in particular ischaemic pain, which comprises administering a compound of formula (V) to a subject in need of such prevention, treatment, or amelioration.

It has also been appreciated that compounds of formula (I)-(IV) may be effective in the prevention, treatment, or amelioration of ischaemic pain.

The term "ischaemic pain" is used herein to mean pain associated with a reduction in blood supply to a part of the body. A reduced blood supply limits the supply of oxygen (hypoxia) and energy to that part of the body. Ischaemia arises from poor blood perfusion of tissues and so ischaemic pain arises in coronary artery disease, peripheral artery disease, and conditions which are characterized by insufficient blood flow, usually secondary to atherosclerosis. Other vascular disorders can also result in

ischaemic pain. These include: left ventricular hypertrophy, coronary artery disease, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncope, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, and exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterans), arteritis, diastolic dysfunction and systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (both Types I and II), thromboembolisms. Haemorrhagic accidents can also result in ischaemic pain. In addition poor perfusion can result in neuropathic and inflammatory pain arising from hypoxia-induced nerve cell damage (e.g. in cardiac arrest or bypass operation, diabetes or neonatal distress).

Compounds of formulae (I)-(V) are believed to be effective in prevention, treatment, or amelioration of ischaemic pain even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. At these doses, it is believed that the compounds do not cause the significant side effects associated with administration of higher doses of spongiosine, or other adenosine receptor agonists.

There is further provided according to the invention use of a compound of the invention (i.e. a compound of formula (I), (II), (III), (IV), or (V)) for the manufacture of a medicament for the prevention, treatment, or amelioration of inflammation.

There is further provided according to the invention a method of prevention, treatment, or amelioration of inflammation, which comprises administering a compound of the invention to a subject in need of such prevention, treatment, or amelioration.

In particular, it is believed that compounds of the invention (i.e. compounds of formula (I), (II), (III), (IV), or (V)) can be used to prevent, treat, or ameliorate inflammation caused by or associated with: cancer (such as leukemias, lymphomas, carcinomas, colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and

prostate metastases, etc.); auto-immune disease (such as organ transplant rejection, lupus erythematosus, graft v. host rejection, allograft rejections, multiple sclerosis, rheumatoid arthritis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes); autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis); obesity; cardiovascular conditions associated with poor tissue perfusion and inflammation (such as atheromas, atherosclerosis, stroke, ischaemia-reperfusion injury, claudication, spinal cord injury, congestive heart failure, vasculitis, haemorrhagic shock, vasospasm following subarachnoid haemorrhage, vasospasm following cerebrovascular accident, pleuritis, pericarditis, the cardiovascular complications of diabetes); ischaemia-reperfusion injury, ischaemia and associated inflammation, restenosis following angioplasty and inflammatory aneurysms; epilepsy, neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), fibrosis (for example of the lung, skin and liver), multiple sclerosis, sepsis, septic shock, encephalitis, infectious arthritis, Jarisch-Herxheimer reaction, shingles, toxic shock, cerebral malaria, Lyme's disease, endotoxic shock, gram negative shock, haemorrhagic shock, hepatitis (arising both from tissue damage or viral infection), deep vein thrombosis, gout; conditions associated with breathing difficulties (e.g. chronic obstructive pulmonary disease, impeded and obstructed airways, bronchoconstriction, pulmonary vasoconstriction, impeded respiration, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, bronchial allergy and/or inflammation, asthma, hay fever, rhinitis, vernal conjunctivitis and adult respiratory distress syndrome); conditions associated with inflammation of the skin (including psoriasis, eczema, ulcers, contact dermatitis); conditions associated with inflammation of the bowel (including Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, inflammatory bowel disease); HIV (particularly HIV infection), cerebral malaria, bacterial meningitis, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, osteoporosis and other bone resorption diseases, osteoarthritis, rheumatoid arthritis, infertility from endometriosis, fever and myalgia due to infection, cachexia secondary to cancer, cachexia secondary to infection or malignancy, cachexia secondary to acquired

immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment, and other conditions mediated by excessive anti-inflammatory cell (including neutrophil, eosinophil, macrophage and T- cell) activity.

Continuous low grade inflammation is known to be associated with obesity (in the presence and absence of insulin resistance and Type II diabetes) (Browning et al (2004) Metabolism 53, 899-903, Inflammatory markers elevated in blood of obese women; Mangge et al (2004) Exp Clin Endocrinol Diabetes 112, 378-382, Juvenile obesity correlates with serum inflammatory marker C-reactive protein; Maachi et al Int J Obes Relat Metab Disord. 2004 28, 993-997, Systemic low grade inflammation in obese people). A possible reason for this is that fat cells secrete TNF alpha and interleukins 1 and 6, which are pro-inflammatory.

Compounds of the invention that are selective agonists of adenosine A2A and/or A3 receptors are particularly preferred because it is believed that such compounds will have strong anti-inflammatory activity. By selective agonists of adenosine A2A and/or A3 receptors is meant agonists that activate adenosine A2A and/or A3 receptors at concentrations that are lower (preferably one thousandth to one fifth) than required to activate adenosine A1 receptors. Furthermore, A1 receptors have pro-inflammatory activity, so such effects are expected to be minimised for compounds that are selective for A2A and/or A3 receptors.

It will be appreciated that any pathological condition that can be prevented or improved by agonism of adenosine A2A and/or A3 receptors can be prevented, treated, or ameliorated by compounds of formulae (I)-(V).

According to the invention there is provided use of a compound of formula (I)-(V) in the manufacture of a medicament for the prevention, treatment, or amelioration of a pathological condition that can be improved or prevented by agonism of adenosine A2A and/or A3 receptors.

There is also provided according to the invention a method of prevention, treatment, or amelioration of a pathological condition that can be improved or prevented by agonism of adenosine A2A and/or A3 receptors, which comprises administering a compound of formula (I)-(V) to a subject in need of such prevention, treatment, or amelioration.

A person of ordinary skill in the art can readily test whether or not a pathological condition that is prevented, treated, or ameliorated by a compound of formula (I)-(V) is acting via adenosine A2A and/or A3 receptors. For example, this may be done by comparing the effect of the compound in an animal model of the pathological condition in the presence and absence of a selective antagonist of an adenosine A2A and/or A3 receptor. If the effect of the compound in the presence of the antagonist is reduced or absent compared with the effect of the compound in the absence of the antagonist, it is concluded that the compound is exerting its effect via an adenosine A2A and/or A3 receptor. Antagonists of adenosine A2A and A3 receptors are known to those of ordinary skill in the art (see for example Ongini *et al.*, *Farmacol.* 2001 Jan-Feb;56(1-2):87-90; Muller, *Curr Top Med Chem.* 2003;3(4):445-62).

Alternatively, an adenosine A2A receptor knockout mouse may be used (Ohta A and Sitkovsky M, *Nature* 2001;414:916-20). For example, the effect of the compound on a mouse that has symptoms of the pathological condition is compared with its effect on an adenosine A2A knockout mouse that has corresponding symptoms. If the compound is only effective in the mouse that has adenosine A2A receptors it is concluded that the compound is exerting its effect via adenosine A2A receptors.

Compounds of the invention (i.e. compounds of formula (I), (II), (III), (IV), or (V)) are believed to be much more effective at low doses than other adenosine receptor agonists. Thus, it is expected that compounds of the invention can be effectively administered at doses at which they have reduced probability and severity of side effects, or at which side effects are not observed. Such compounds provide significant advantages over the vast majority of other adenosine receptor agonists which only have anti-inflammatory effects at the same concentrations at which serious side effects are observed.

Compounds of the invention may alternatively or additionally have reduced probability and severity of side effects compared to other adenosine receptor agonists.

It is also believed that compounds of the invention (i.e. compounds of formula (I), (II), (III), (IV), or (V)) may be effective as disease-modifying anti-rheumatic drugs (DMARDs), in particular for use in the prevention, treatment, or amelioration of rheumatoid arthritis, and possibly other arthropathies such as osteoarthritis.

Medications used to treat rheumatoid arthritis (RA) can be divided into two groups: those that help relieve RA symptoms; and those that help modify the disease. Drugs that help to relieve RA symptoms include nonsteroidal anti-inflammatory drugs (NSAIDs) that relieve pain and reduce inflammation in the affected joints, analgesics (such as acetaminophen and narcotic pain medications) that relieve pain but do not slow joint damage or reduce inflammation, and corticosteroids that are anti-inflammatory drugs.

DMARDs help to improve RA symptoms (such as joint swelling and tenderness), but also slow the progression of joint damage caused by RA. Thus, while there is no cure for RA, DMARDs help to slow the progression of RA. In the past DMARDs were usually used to treat RA after NSAID therapy failed. However, DMARDs are now beginning to be used earlier in the course of RA because studies have suggested that early intervention with DMARDs offers important benefits. DMARDs and NSAIDs are often used in combination with each other.

Results from clinical studies have shown that known DMARDs slow the progression of RA. After 6 months of treatment, the rate of bone and cartilage damage had already started to slow in patients' joints. After 1 year, patients showed very little progression of joint damage, and after 2 years X rays showed that few patients in the study had newly damaged joints during the second year of treatment.

Examples of known DMARDs include sulphasalazine, penicillamine, chloroquine, hydroxychloroquine, gold (by intramuscular injection or orally as auranofin), methotrexate, cyclosporin, azathioprine, cyclophosphamide, leflunomide. More recently biological DMARDs have been developed which inhibit tumour necrosis factor alpha (TNF alpha). One example is Humira® which is indicated for reducing signs and symptoms and inhibiting the progression of structural damage in adults with moderately to severely active RA who have had an inadequate response to one or more DMARDs. Humira® is an anti-TNF alpha antibody.

Many of the known DMARDs cause serious side effects. Consequently, it is desired to provide new DMARDs that can be administered with minimal side effects.

Example 11 below shows the ability of spongostin to reduce phorbol ester induced TNF alpha release in U937 human macrophage cells. On this basis, it is believed that spongostin and related compounds of formula (I), (II), (III), (IV), or (V) also have DMARD activity.

According to the invention there is provided use of a compound of formula (I), (II), (III), (IV), or (V) in the manufacture of a medicament for slowing the progression of arthropathy.

There is also provided according to the invention a method of slowing the progression of arthropathy, which comprises administering a compound of formula (I), (II), (III), (IV), or (V) to a subject in need thereof.

Preferably the progression of RA is slowed, and in particular the progression of joint damage caused by RA.

A compound of the invention may be administered to the subject at any stage in the course of RA. A compound of the invention may be administered in combination with one or more NSAIDs or other DMARDs.

Compounds of the invention are believed to be effective as DMARDs even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. At these doses, it is believed that the compounds do not cause the significant side effects associated with administration of higher doses of spongiosine, or other adenosine receptor agonists.

A particular advantage of use of compounds of the invention as DMARDs is that it is believed that they will be orally active, in contrast to anti-TNF alpha antibodies which must be injected.

It has also been appreciated that compounds of formulae (I)-(V) may be effective in preventing, treating, or ameliorating macro and micro vascular complications of type 1 or 2 diabetes (including retinopathy, nephropathy, autonomic neuropathy), or blood vessel damage caused by ischaemia (either diabetic or otherwise) or atherosclerosis (either diabetic or otherwise).

According to the invention, there is provided use of a compound of formula (I), (II), (III), (IV), or (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of macro or micro vascular complications of type 1 or 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis.

According to the invention there is also provided a method of preventing, treating, or ameliorating macro or micro vascular complications of type 1 or 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis, in a subject in need of such prevention, treatment, or amelioration, which comprises administering a compound of formula (I), (II), (III), (IV), or (V) to the subject.

Preferred compounds of formula (V) are 2-methoxyadenosine (i.e. spongiosine), 2-ethoxyadenosine, and 2-butyloxyadenosine.

Compounds of formulae (I)-(V) are believed to be effective in prevention, treatment, or amelioration of macro or micro vascular complications of type 1 and 2 diabetes, including retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis (either diabetic or otherwise)) even when administered at doses expected to give plasma concentrations well below those known to activate adenosine receptors. At these doses, it is believed that the compounds do not cause the significant side effects associated with administration of higher doses of spongosine, or other adenosine receptor agonists.

Compounds of formula (I)-(V) are also believed to be effective in the promotion of wound healing. According to the invention there is provided use of a compound of formula (I), (II), (III), (IV), or (V) in the manufacture of a medicament for the promotion of wound healing. There is also provided according to the invention a method of promoting wound healing in a subject, which comprises administering a compound of formula (I), (II), (III), (IV), or (V) to the subject.

The amount of a compound of formula (I)-(V) that is administered to a subject is preferably an amount which gives rise to a peak plasma concentration that is less than the EC50 value of the compound at adenosine receptors (preferably at pH 7.4).

It will be appreciated that the EC50 value of the compound is likely to be different for different adenosine receptors (i.e. the A1, A2A, A2B, A3 adenosine receptors). The amount of the compound that is to be administered should be calculated relative to the lowest EC50 value of the compound at the different receptors.

Thus, preferably the amount of a compound of the invention that is administered to a subject should be an amount which gives rise to a peak plasma concentration that is less than the lowest EC50 value of the compound at adenosine receptors.

Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one

fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value.

Preferably the amount of a compound of the invention that is administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest EC50 value of the compound at adenosine receptors.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour between one thousandth and one fifth, or one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the EC50 value of the compound at adenosine receptors at pH 7.4.

For the avoidance of doubt, the EC50 value of a compound is defined herein as the concentration of the compound that provokes a receptor response halfway between the baseline receptor response and the maximum receptor response (as determined, for example, using a dose-response curve).

The EC50 value should be determined under standard conditions (balanced salt solutions buffered to pH 7.4). For EC50 determinations using isolated membranes, cells and tissues this would be in buffered salt solution at pH 7.4 (e.g. cell culture medium), for example as in Daly *et al.*, Pharmacol. (1993) 46, 91-100), or preferably as in Tilburg *et al* (J. Med. Chem. (2002) 45, 91-100). The EC50 could also be determined *in vivo* by measuring adenosine receptor mediated responses in a normal healthy animal, or even in a tissue perfused under normal conditions (i.e. oxygenated blood, or oxygenated isotonic media, also buffered at pH 7.4) in a normal healthy animal.

Alternatively, the amount of a compound of the invention that is administered may be an amount that results in a peak plasma concentration that is less than the lowest or

highest K_d value of the compound at adenosine receptors (i.e. less than the lowest or highest K_d value of the compound at A1, A2A, A2B, and A3 adenosine receptors). Preferably the peak plasma concentration of the compound is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one third, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the lowest or highest K_d value.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for at least one hour between one thousandth and one fifth, more preferably between one thousandth and one twentieth, or one hundredth and one fifth, or one fiftieth and one fifth, of the K_d value of the compound at adenosine receptors.

Preferably the amount of the compound that is administered is an amount that results in a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one fiftieth to one third, or one tenth to one fifth) of the lowest or highest K_d value of the compound at adenosine receptors.

The K_d value of the compound at each receptor should be determined under standard conditions using plasma membranes as a source of the adenosine receptors derived either from tissues or cells endogenously expressing these receptors or from cells transfected with DNA vectors encoding the adenosine receptor genes. Alternatively whole cell preparations using cells expressing adenosine receptors can be used. Labelled ligands (e.g. radiolabelled) selective for the different receptors should be used in buffered (pH7.4) salt solutions (see e.g. Tilburg et al, J. Med. Chem. (2002) 45, 420-429) to determine the binding affinity and thus the K_d of the compound at each receptor.

Alternatively, the amount of a compound of the invention that is administered may be an amount that is one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount (or dose) of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum amount of the compound that gives rise to the side effects.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth of the minimum dose that gives rise to the side effects.

Alternatively, the amount of a compound of the invention that is administered may be an amount that gives rise to plasma concentrations that are one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one third, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that cause bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered. Preferably the amount administered gives rise to a plasma concentration that is maintained for more than one hour at one ten thousandth to one fifth (or one ten thousandth to one twentieth, or one ten thousandth to one hundredth, or one ten thousandth to one thousandth, or one thousandth to one fifth, or

one thousandth to one twentieth, or one fiftieth to one tenth, or one hundredth to one fifth, or one fiftieth to one fifth, or one tenth to one fifth) of the minimum plasma concentration of the compound that causes the side effects.

Preferably the amount administered gives rise to a plasma concentration that is maintained for more than 1 hour between one thousandth and one twentieth, or one hundredth or one fiftieth and one fifth, of the minimum plasma concentration that causes the side effects.

It is expected that the amount of a compound of the invention that is administered should be 0.001-15 mg/kg. The amount may be less than 6 mg/kg. The amount may be at least 0.001, 0.01, 0.1, or 0.2 mg/kg. The amount may be less than 0.1, or 0.01 mg/kg. Preferred ranges are 0.001-10, 0.001-5, 0.001-2, 0.001-1, 0.001-0.1, 0.001-0.01, 0.01-15, 0.01-10, 0.01-5, 0.01-2, 0.01-1, 0.1-10, 0.1-5, 0.1-2, 0.1-1, 0.2-15, 0.2-10, 0.2-5, 0.2-2, 0.2-1.2, 0.2-1, 0.6-1.2, mg/kg.

Preferred doses for a human subject (for example a 70kg subject) are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7-70mg, or 14-70mg.

It is believed that the dosage amounts specified above are significantly lower (up to approximately 1000 times lower) than would be expected to be required for an analgesic or an anti-inflammatory effect based on the EC50 value of the compound at the adenosine A2A receptor.

The dosage amounts specified above are aimed at producing plasma concentrations that are approximately one thousandth to one hundredth of the EC50 value of spongostin at the adenosine A1 receptor.

The appropriate dosage of a compound of the invention will vary with the age, sex, weight, and condition of the subject being treated, the potency of the compound, and the route of administration, etc. The appropriate dosage can readily be determined by one skilled in the art.

A compound of the invention may be administered with or without other therapeutic agents, for example analgesics or anti-inflammatories (such as opiates, steroids, NSAIDs, cannabinoids, tachykinin modulators, or bradykinin modulators) or anti-hyperalgesics (such as gabapentin, pregabalin, cannabinoids, sodium or calcium channel modulators, anti-epileptics or anti-depressants), or DMARDs.

In general, a compound of the invention may be administered by known means, in any suitable formulation, by any suitable route. A compound of the invention is preferably administered orally, parenterally, sublingually, transdermally, intrathecally, or transmucosally. Other suitable routes include intravenous, intramuscular, subcutaneous, inhaled, and topical. The amount of drug administered will typically be higher when administered orally than when administered, say, intravenously.

It will be appreciated that a compound of the invention may be administered together with a physiologically acceptable carrier, excipient, or diluent.

Suitable compositions, for example for oral administration, include solid unit dose forms, and those containing liquid, e.g. for injection, such as tablets, capsules, vials and ampoules, in which the active agent is formulated, by known means, with a physiologically acceptable excipient, diluent or carrier. Suitable diluents and carriers are known, and include, for example, lactose and talc, together with appropriate binding agents etc.

A unit dosage of a compound of the invention (i.e. a compound of formula (I), (II), (III), IV), or (V)) typically comprises up to 500 mg (for example 1 to 500 mg, or (preferably) 5 to 500 mg) of the active agent. Preferably the active agent is in the form of a pharmaceutical composition comprising the active agent and a physiologically acceptable carrier, excipient, or diluent. The preferred dosage is 0.1 to 2, e.g. 0.5 to 1, typically about 0.2 or 0.6, mg of the active agent per kg of the (human) subject. Preferred amounts of the active agent are less than 420mg, preferably at least 0.7mg, more preferably at least 3.5mg, most preferably at least 7mg. More preferably 7 to 70mg, or 14 to 70mg. At these levels, it is believed that

effective treatment can be achieved substantially without a concomitant fall (for example, no more than 10%) in blood pressure.

A unit dosage of a compound of the invention may further comprise one or more other therapeutic agents, for example analgesics, anti-inflammatories, anti-hyperalgesics, or DMARDs.

Preferably a compound of the invention is administered at a frequency of 2 or 3 times per day.

Compounds of the invention can also serve as a basis for identifying more effective drugs, or drugs that have further reduced side effects.

Examples of pharmaceutically acceptable salts are organic addition salts formed with acids which form a physiologically acceptable anion, for example, tosylate, methanesulphonate, malate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α -ketoglutarate, and α -glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulphate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium, or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

Use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain, or a method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (I) in accordance with the invention may exclude prevention, treatment, or amelioration of pain resulting from damage caused to organs as a consequence of reperfusion following an ischaemic episode, for example a myocardial infarct, or a stroke.

Use of a compound of formula (V) in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain in accordance with the invention may exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

A method of prevention, treatment, or amelioration of ischaemic pain by administering a compound of formula (V) in accordance with the invention may exclude use of 2-propoxyadenosine, 2-isopropoxyadenosine, 3' deoxy 2 methoxyadenosine or 3' deoxy 2 ethoxyadenosine.

Embodiments of the invention are described in the following examples with reference to the accompanying drawings in which:

Figure 1 shows the effect of spongiosine (0.6 mg/kg p.o.) on A: blood pressure in normal rats; B: heart rate;

Figure 2 shows the change in plasma concentration over time after administration of spongiosine

Figure 3 shows the anti-hyperalgesic actions of spongiosine (0.6 mg/kg p.o.) on carrageenan induced hyperalgesia. A: time course (* $p < 0.05$, ** $p < 0.01$ versus vehicle (Sidak's), $p > 0.05$ versus BL over 5 hrs for Spongiosine and IND (Dunnett's)); B: dose dependency of the anti-hyperalgesic effect;

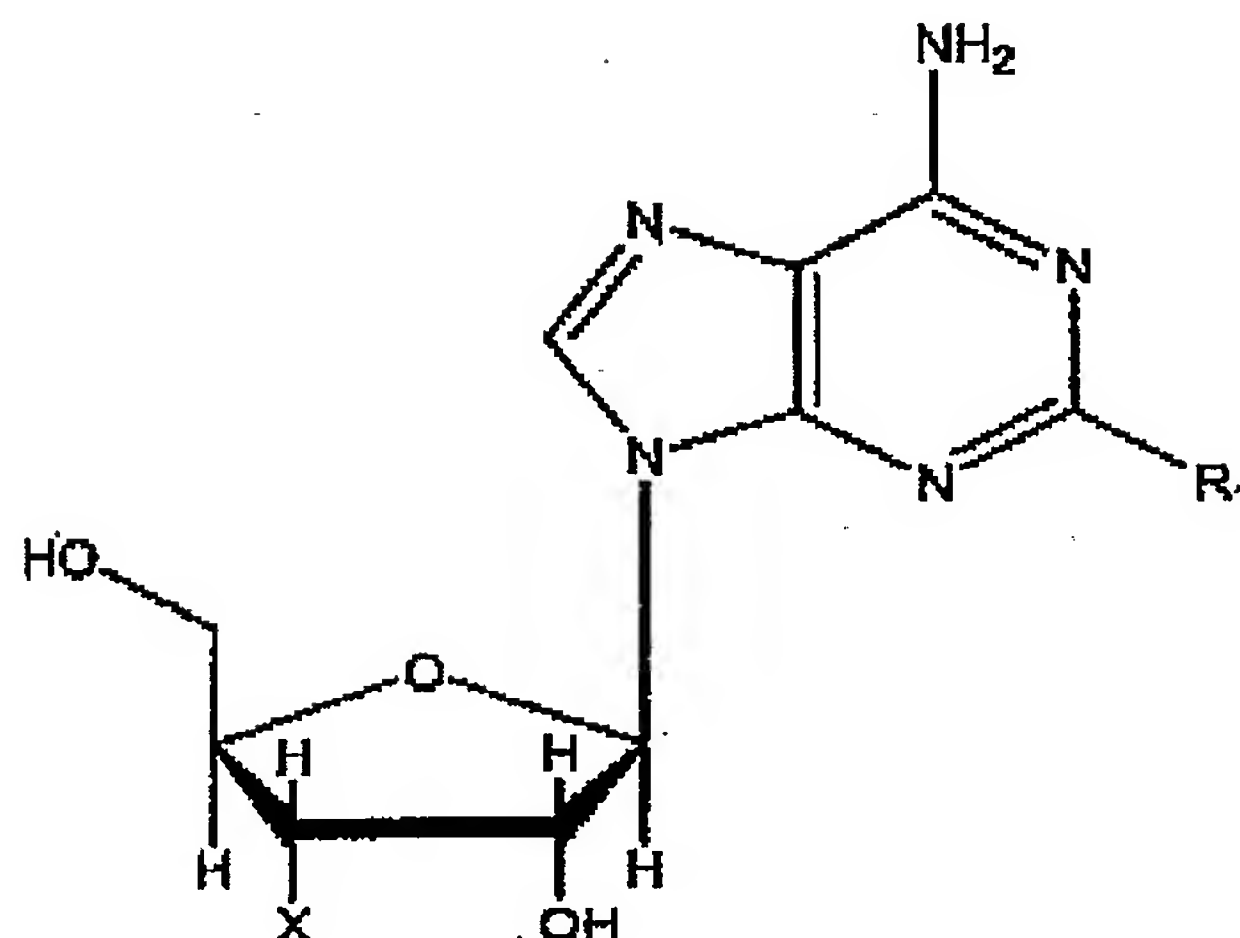
Figure 4 shows the anti-hyperalgesic actions of spongiosine (0.6 mg/kg p.o.) in the chronic constriction injury model of neuropathic pain (* $p < 0.05$, ** $p < 0.01$ vs veh (ANOVA Sidak's);

Figure 5 shows the effect of spongiosine (0.6 mg/kg p.o.) in the presence and absence of naloxone in the chronic constriction injury model of neuropathic pain;

Figure 6 shows the additive effect of spongiosine and gabapentin in the chronic constriction injury model of neuropathic pain; and

Figure 7 shows the effect of spongiosine on LPS induced TNF alpha release in cells of human macrophage cell line U937.

Structures of preferred compounds of the invention are given in the Examples below. A K_i value is given for each compound. To calculate this, rat striatal membranes were incubated for 90 minutes at 22°C in the presence of 2nM [3H]-CGS21680, 1Unit/ml adenosine deaminase and increasing concentrations of the compound being studied, prior to filtration and liquid scintillation counting.

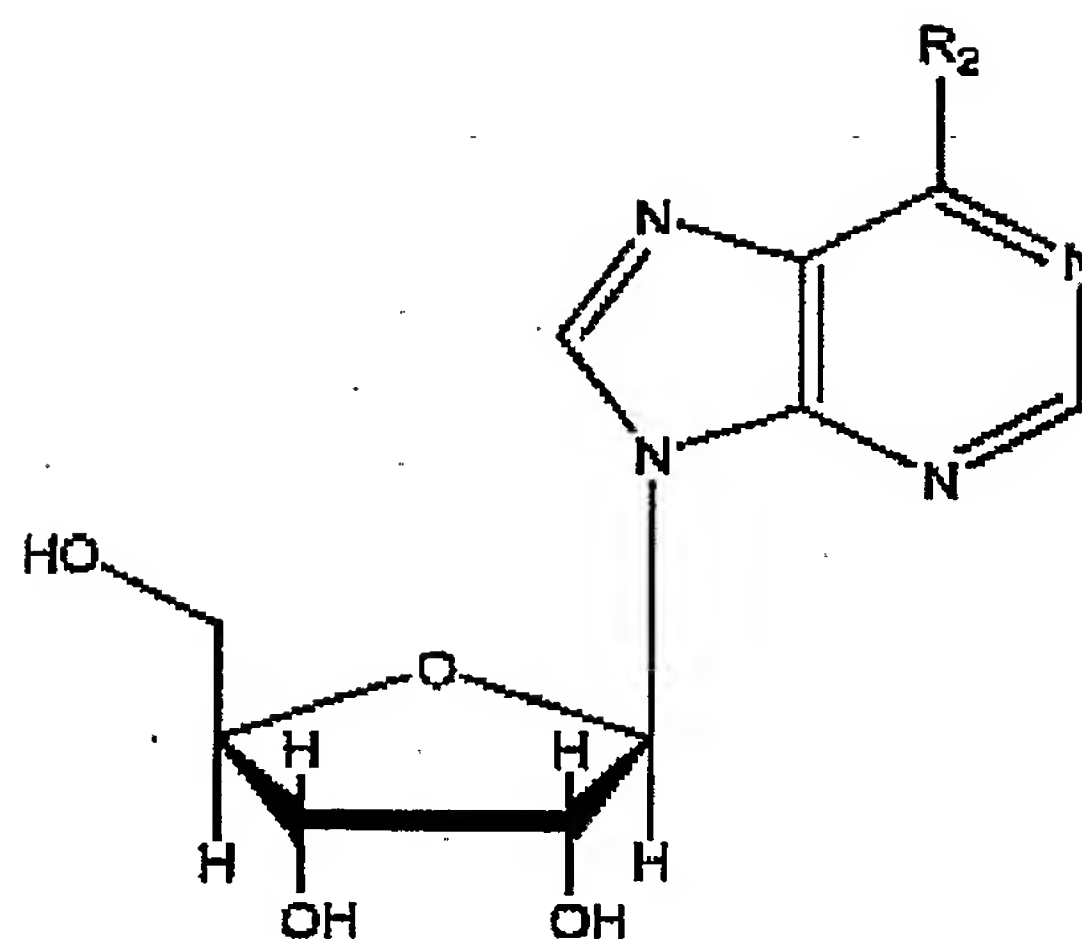
Example 1**When X = OH**

Compound No.	Structure R ₁	(K _i) nM
1	OCH ₃	1300
2	OCH ₂ CH ₂ CH ₂ CH ₃	280
3	O CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	1500
4	OPh	2500
5	O-(4-cyano)Ph	1300
6	O-(3-Ph)Ph	620
7	5-indanyloxy	760
8	O-(3-CH(CH ₃) ₂)Ph	560
9	NH(CH ₃)	1356
10	NHCH ₂ CH ₃	1200
11	N(CH ₃) ₂	13350
12	NHCH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	290
13	NHPh	160
14	NH-(4-MeO)Ph	55
15	NH-(4-F)Ph	200
16	NH-cyclopentyl	420
17	NH-cyclohexyl	1000

18	N-CH ₃ , N-CH ₂ CH ₂ CH(CH ₃) ₂	4000
19	OCH ₂ cyclopentyl	200
20	SO ₂ CH ₂ CH ₃	39000
21	OCH ₂ CH ₂ OH	203
22	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	800

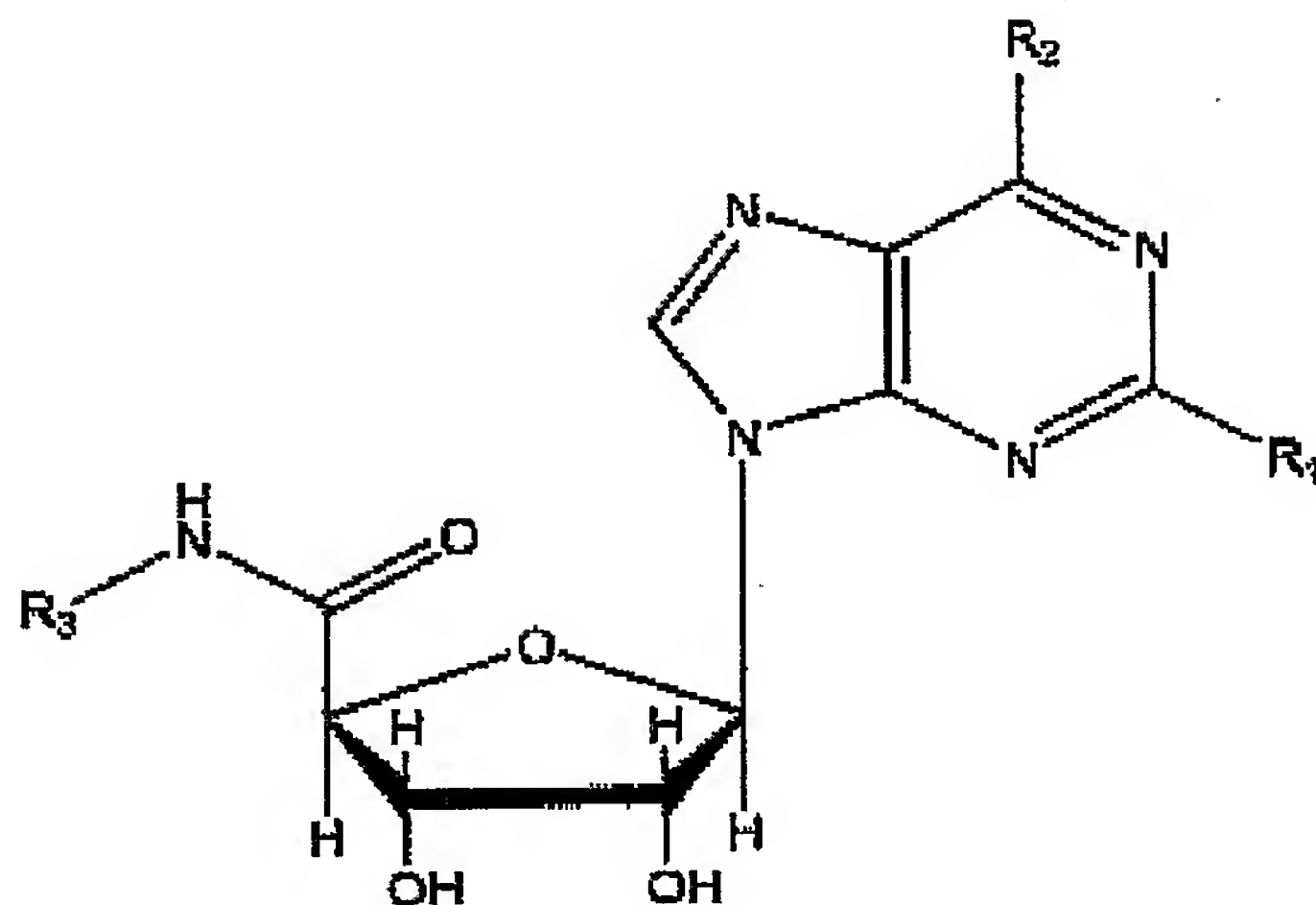
When X = H

Compound No.	Structure R ₁	(K _i) nM
23	O CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	2990

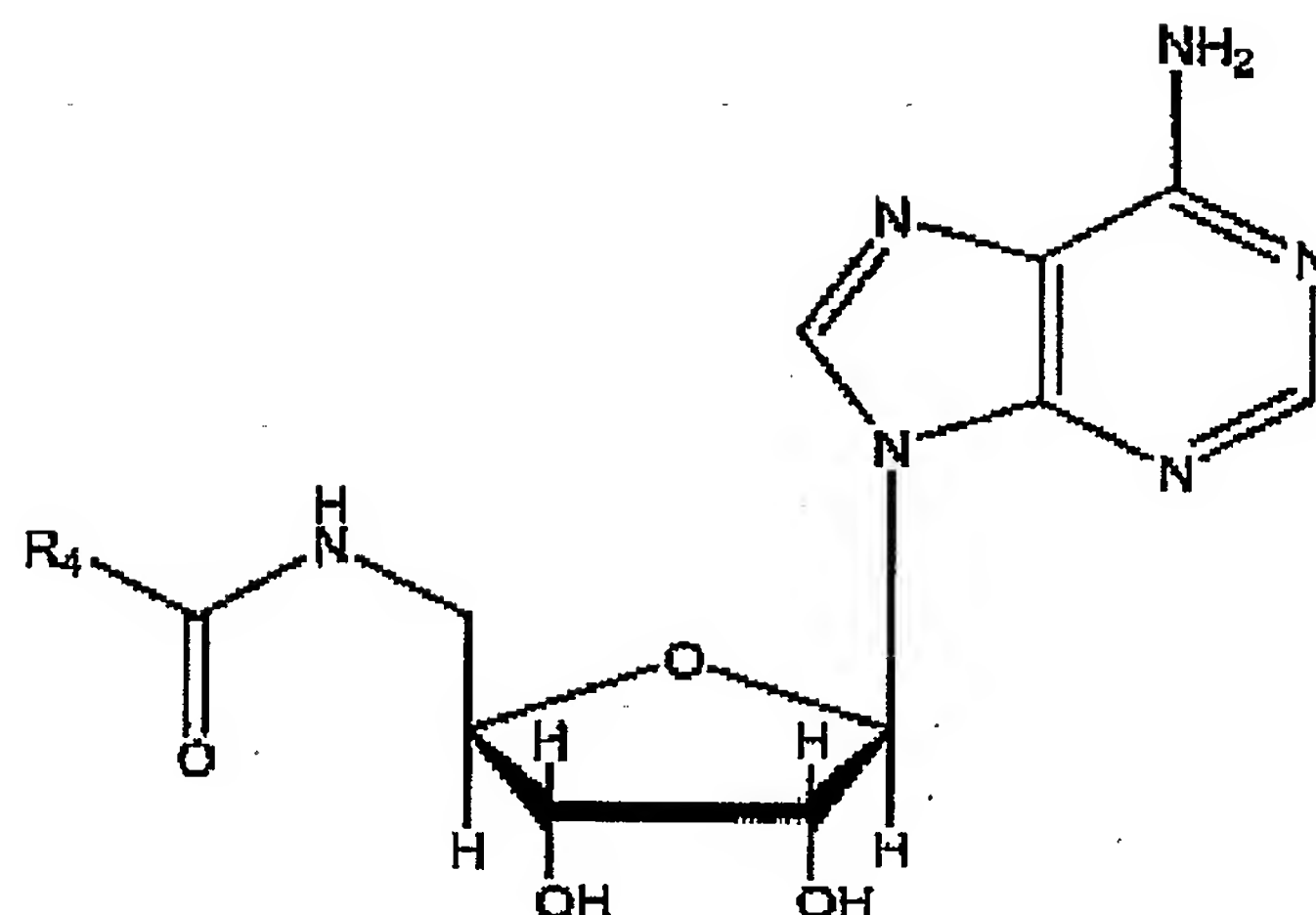
Example 2

Compound No.	Structure R ₂	(K _i) nM
24	N(CH ₃) ₂	450000
25	NHCH ₂ CHC(CH ₃) ₂	8600
26	N-CH ₃ , N-CH ₂ Ph	18500
27	Piperazinyl	5000
28	N-Me, N-(CH ₂ CH ₂ OCH ₃)	13000

Example 3



Compound No.	R ₁	R ₂	R ₃	(K _i) nM
29	H	NH ₂	CH(CH ₃) ₂	1930
30	H	NH ₂	H	270
31	H	NHCH ₃	CH(CH ₃) ₂	2440
32	OCH ₃	NH ₂	Ph	26100

Example 4

Compound No.	Structure R ₄	(K _i) nM
33	CH ₂ CH ₂ CH ₃	16900
34	NHCH ₂ CH ₃	6570

Example 5

Figure 1: Spongiosine (0.624 mg/kg p.o.) has no significant effect on blood pressure or heart rate. An implantable radiotelemetry device was placed in the abdominal cavity of 6 rats per group. The pressure catheter of the device was inserted in the abdominal aorta and two electrodes tunnelised under the skin in a lead II position (left side of abdominal cavity/right shoulder). Individual rats were placed in their own cage on a radioreceptor (DSI) for data acquisition. A: blood pressure; B: heart rate.

Example 6

The EC₅₀ value of spongiosine at adenosine receptors (measured at pH7.4) is 900ng/ml (3 μ M). Figure 2 shows the change in plasma concentration over time after administration of spongiosine at 0.6 mg/kg to a rat. It can be seen that the plasma concentration remains above 2% of the EC₅₀ value for more than 3 hours. Anti-hyperalgesic effects have been observed (without blood pressure changes) when the

peak plasma concentration is between 1% and 30% of the EC50 value determined in vitro. If the peak plasma concentration reaches the EC50 value profound reductions in blood pressure occur that last for hours.

Example 7

Figure 3: A. Spongostine (0.624mg/kg p.o.) inhibits carrageenan (CGN) induced thermal hyperalgesia (CITH) with comparable efficacy to indomethacin (3mg/kg, po). B. Concentration-response relationship for Spongostine at 3 hrs post dosing. Carrageenan (2%, 10 microlitres) was administered into the right hind paw. A heat source was placed close to the treated and untreated hind paws, and the difference in the paw withdrawal latencies is shown. Spongostine was administered at the same time as carrageenan.

Example 8

Figure 4: Spongostine (0.624mg/kg p.o.) inhibits thermal hyperalgesia caused by chronic constriction injury of the rat sciatic nerve. Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed thermal hyperalgesia in the operated leg as judged by the difference in paw withdrawal latencies of the right and left paws. Administration of spongostine reduced the hyperalgesia as shown by the reduction in the difference between the withdrawal latencies. Spongostine was as, or more, effective than carbamazepine (CBZ, 100mg/kg s.c.)

Example 9

Figure 5: Spongostine (1.2 mg/kg p.o.) inhibits static allodynia caused by chronic constriction injury of the rat sciatic nerve, both in the presence and absence of naloxone (1 mg/kg s.c.). Under anaesthesia the sciatic nerve was displayed in the right leg, and four loose ligatures tied round the nerve bundle. After approximately two weeks the rats developed static allodynia in the operated leg as judged by the difference in paw withdrawal thresholds of the right and left paws. Administration of spongostine reduced the hyperalgesia as shown by the increased paw withdrawal threshold (PWT) in the presence and absence of naloxone. Veh: vehicle.

Example 10

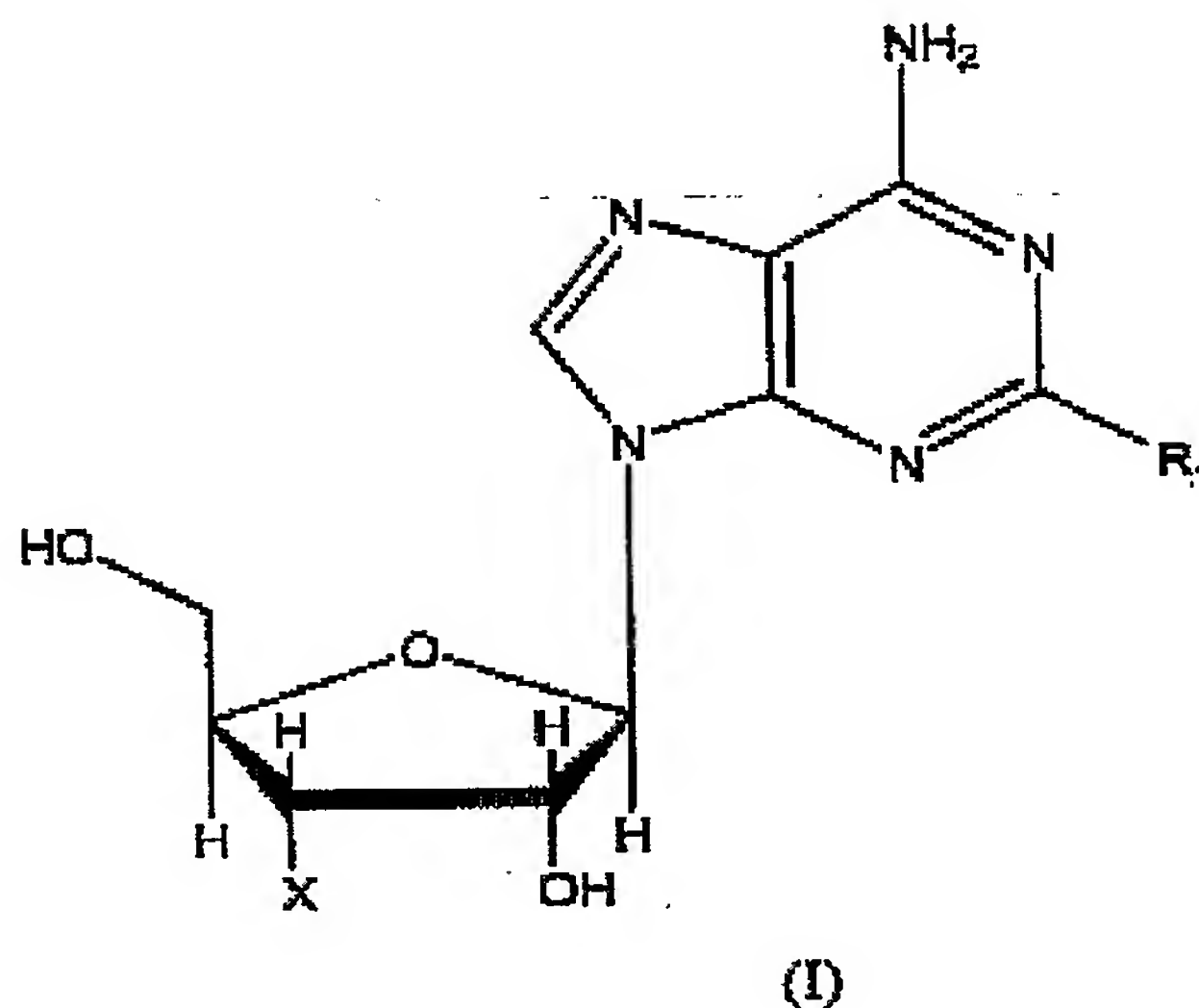
Figure 6: Spongostin and gabapentin inhibit static allodynia caused by chronic constriction injury of the rat sciatic nerve. Spongostin and gabapentin were administered (p.o.) in different proportions as indicated in the drawing. The total dose administered is shown on the horizontal axis, and the paw withdrawal threshold (PWT) on the vertical axis. The predicted anti-hyperalgesic effect (derived from the dose response curves obtained with each agent alone) if the effects of the two compounds are additive is shown (■). The observed effects are indicated by (■). It is apparent that the observed effects are not significantly different from those predicted by additivity.

Example 11

Cells of human macrophage cell line U937 were grown in suspension to 500,000 cells/ml, plated out into 48 well plates, treated with 20ng/ml PMA and incubated for 8 hours. Cells adhered to well bottoms and were washed and allowed to recover for 36 hours before use. Plates were preincubated with concentrations of spongostin, and 100ng/ml of LPS was added 10 minutes later to stimulate TNF production. After 3 hours the cell supernatants were assayed for TNF alpha using fluorescence labeled ELISA kits. A graph showing the results (inhibition of TNF alpha release against spongostin concentration) is shown in Figure 7. The results show that spongostin inhibits LPS induced TNF release, and that this inhibition is sensitive to adenosine receptor inhibitors.

Claims

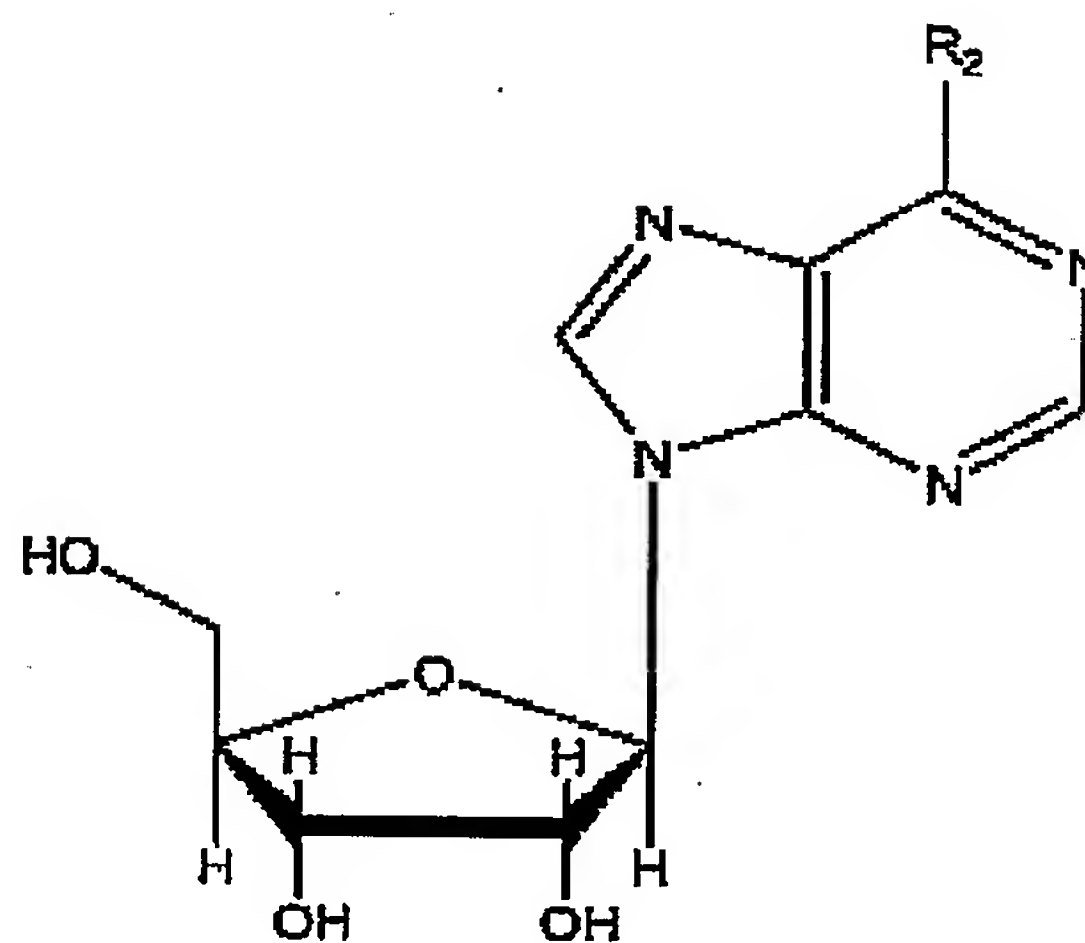
1. A compound of formula (I), (II), (III), or (IV):



wherein:

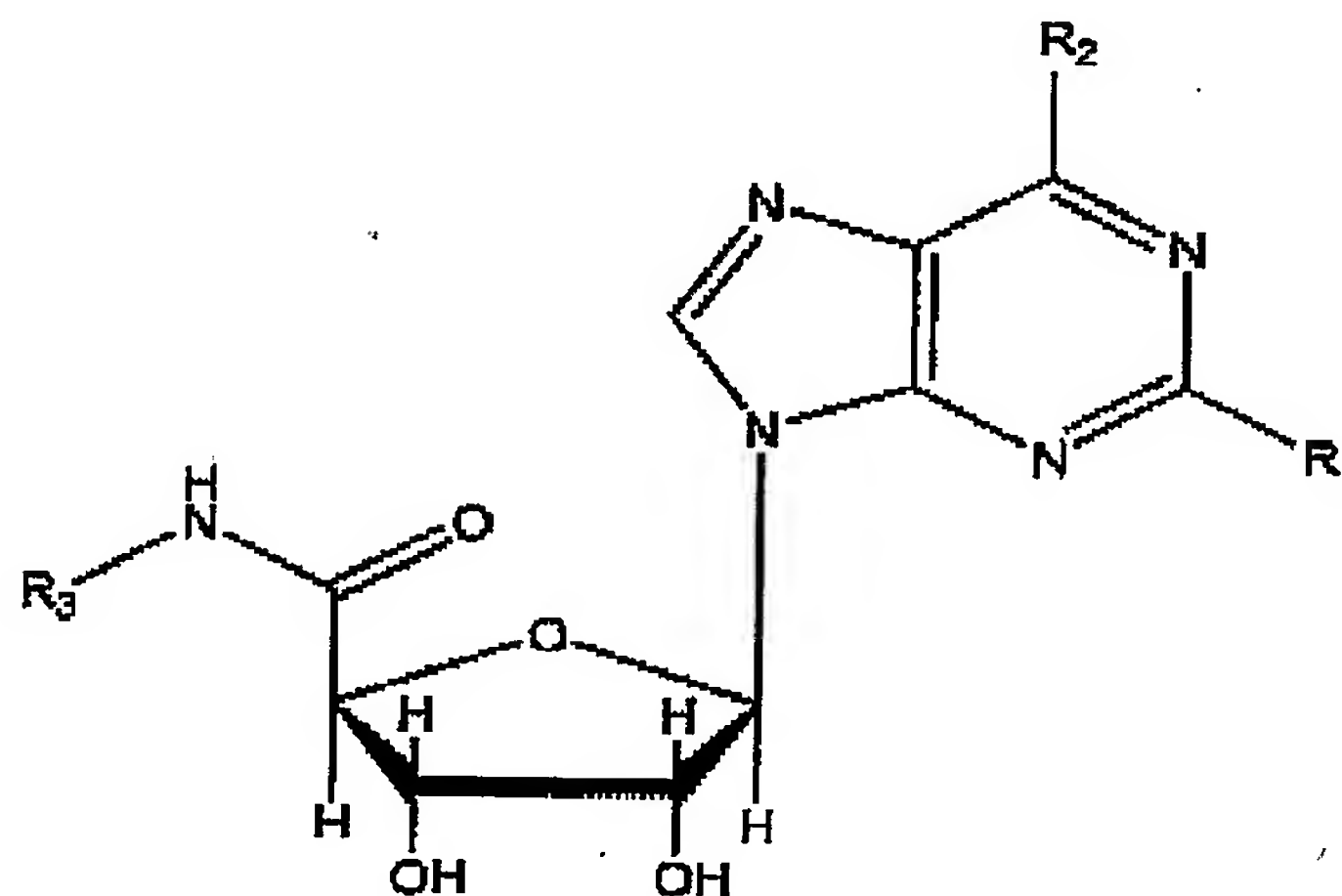
when $X = OH$, R_1 is C_5 - C_6 alkoxy, phenoxy, substituted phenoxy (preferably substituted with nitrile, phenyl or 3-isopropyl), (5-indanyl)oxy, C_1 , C_2 , C_5 , or C_6 alkylamino (straight chain or cyclic), phenylamino with either methoxy or fluoro substituents, (N-methyl, N-isoamylamino), a C_2 sulfone group, a C_7 alkyl group, or OCH_2CH_2OH ; or

when $X = H$, R_1 is *n*-hexyloxy;



(II)

wherein R_2 is NMe_2 , N -(2-isopentenyl), piperazinyl, (N-Me, N-benzyl) or (N-Me, N-(2-methoxyethyl));



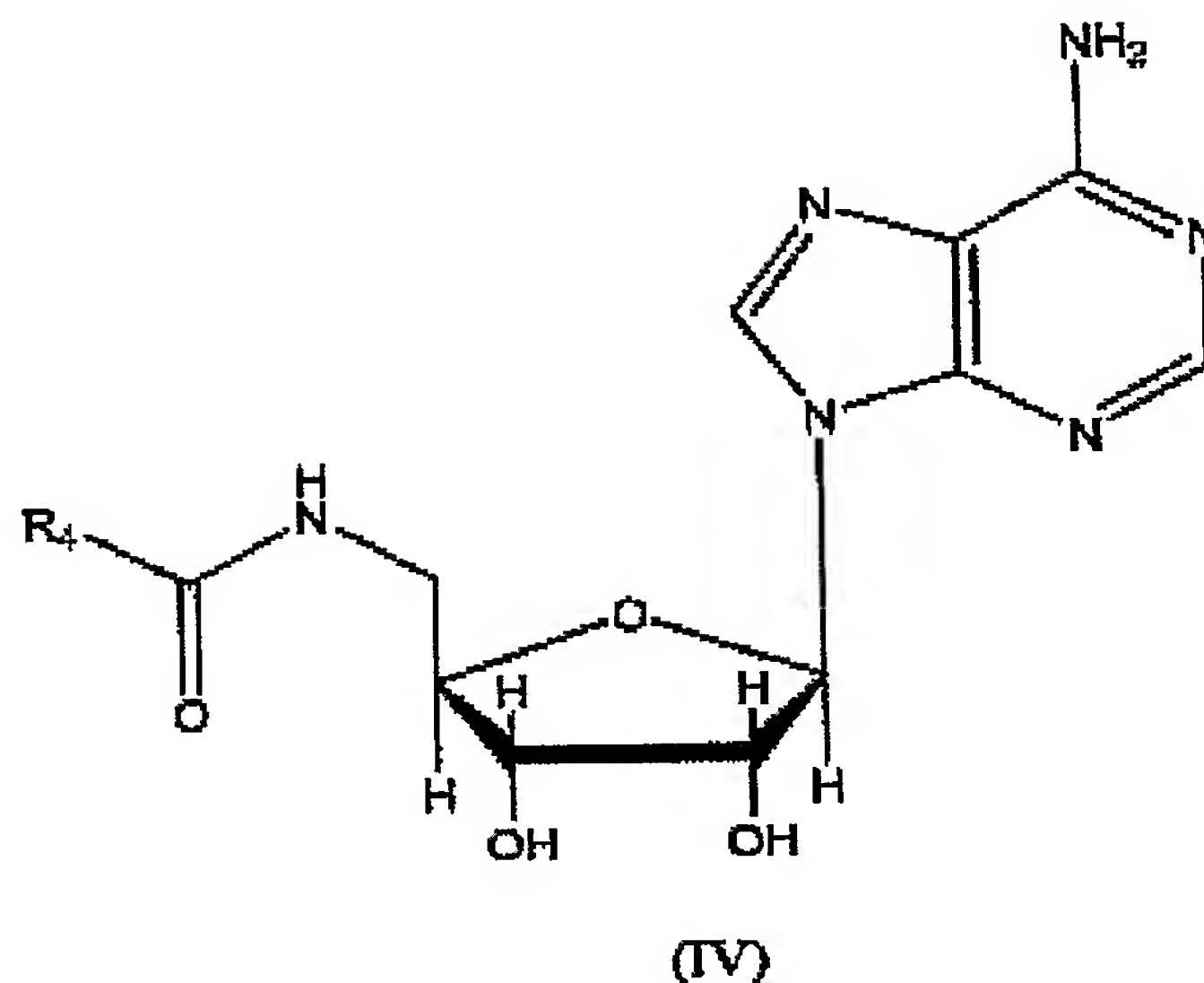
(III)

wherein:

when $R_1 = H$, R_3 is an isopropyl group, and R_2 is either NH_2 or a methylamino group ($NHMe$); or

when $R_1 = H$, R_3 is H , and R_2 is NH_2 ; or

when R_1 is OMe , R_3 is Ph , and R_2 is NH_2 ;



wherein R_4 is *n*-propyl or $NHCH_2CH_3$;

or a pharmaceutically acceptable salt thereof.

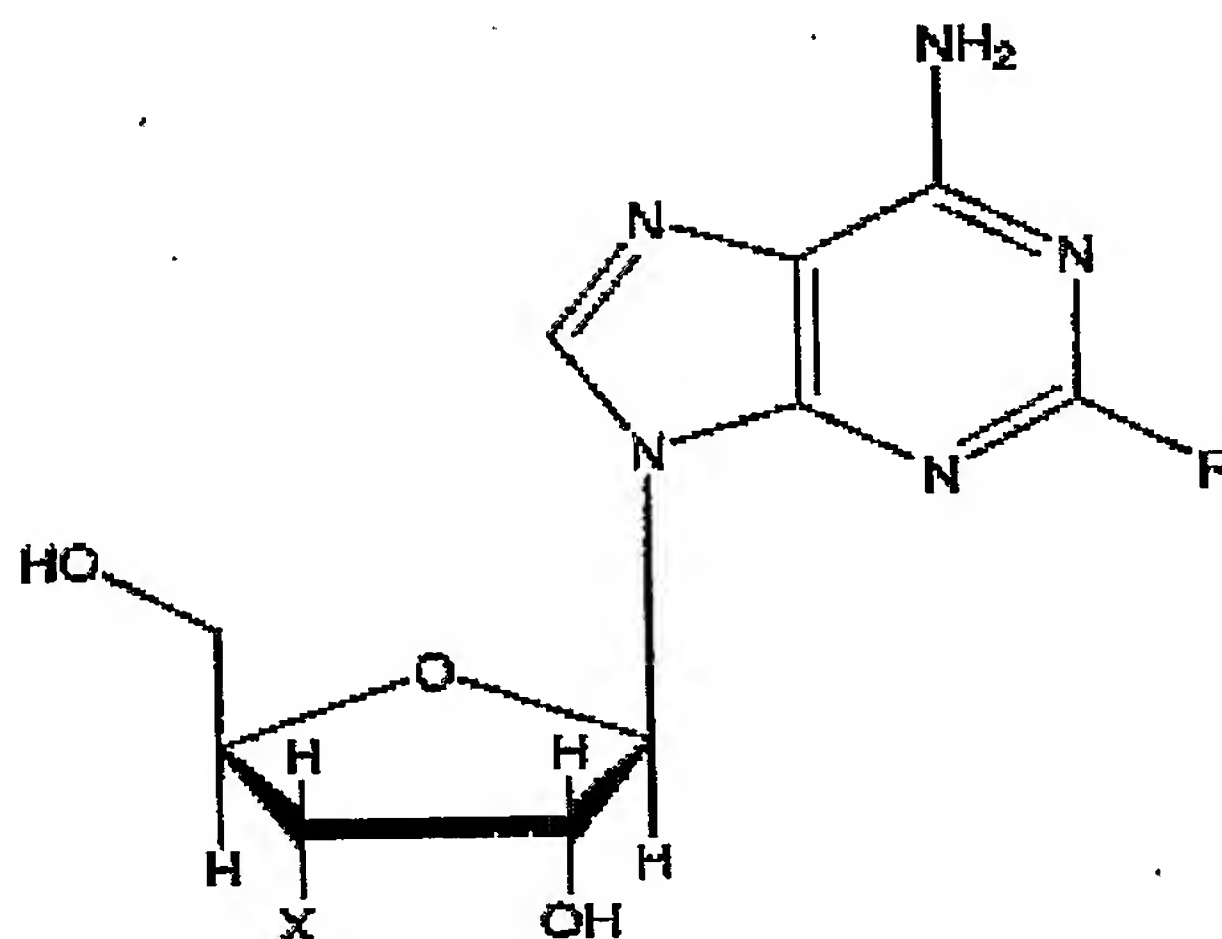
2. A compound according to claim 1 with a structure as defined in any of Examples 1-4, excluding compound 13.
3. A compound according to claim 1 or 2 for use as a medicament.
4. Use of a compound according to claim 1 or 2, or a pharmaceutically acceptable salt of a compound of formula (V) as defined in claim 13, in the manufacture of a medicament for the prevention, treatment, or amelioration of a pathological condition that can be improved or prevented by agonism of adenosine A2A receptors.
5. Use of a compound of formula (V) as defined in claim 13, in the manufacture of a medicament for the prevention, treatment, or amelioration of a pathological condition that can be improved or prevented by agonism of adenosine A2A receptors, excluding pain, cancer, inflammation, auto-immune disease, ischemia-reperfusion injury, epilepsy, sepsis, septic shock, neurodegeneration (including Alzheimer's Disease), muscle fatigue and muscle cramp.

6. Use of a compound according to claim 1 or 2, or compound 13 or a pharmaceutically acceptable salt of compound 13, or a pharmaceutically acceptable salt of a compound of formula (V) as defined in claim 13, in the manufacture of a medicament for the prevention, treatment, or amelioration of pain.
7. Use according to claim 6, wherein the pain is hyperalgesia.
8. Use according to claim 7, wherein the hyperalgesia is neuropathic pain.
9. Use according to any of claims 6 to 8 for the prevention, treatment, or amelioration of: pain associated with cancer, pancreatic pain, pelvic/perineal pain, pain associated with HIV infection, chronic neuropathic pain, lower back pain, failed back surgery pain, back pain, post-operative pain, post physical trauma pain, cardiac pain, chest pain, pelvic pain/PID, joint pain, neck pain, bowel pain, phantom limb pain, obstetric pain, acute herpes zoster pain, acute pancreatitis breakthrough pain, or for the prevention, treatment, or amelioration of neuropathic or other pain caused by, or associated with diabetic neuropathy, polyneuropathy, fibromyalgia, myofascial pain syndrome, osteoarthritis, post herpetic neuralgia, rheumatoid arthritis, sciatica/lumbar radiculopathy, spinal stenosis, temporo-mandibular joint disorder, trigeminal neuralgia, renal colic, dysmenorrhoea/endometriosis.
10. Use according to claim 7, wherein the hyperalgesia is inflammatory pain.
11. Use according to any of claims 6, 7, or 10 wherein the pain is caused by or associated with an inflammatory or immune disease, or as a result of combined inflammatory, autoimmune and neuropathic tissue damage.
12. Use according to any of claims 6, 7, 10, or 11 for the prevention, treatment, or amelioration of bowel pain, pain associated with cancer, back pain, post-operative pain, or for the prevention, treatment, or amelioration of inflammatory or other pain caused by, or associated with rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, cancer, HIV, chronic pulmonary inflammatory disease,

silicosis, pulmonary sarcosis, bone resorption diseases, reperfusion injury, autoimmune damage, graft v. host rejection, allograft rejections, fever and myalgia due to infection, fibromyalgia, AIDS related complex (ARC), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, osteoporosis, cerebral malaria and bacterial meningitis.

13. Use according to claim 6, or use of a compound of formula (V), in the manufacture of a medicament for the prevention, treatment, or amelioration of ischaemic pain:

(V)



wherein: R is C₁₋₄ alkoxy, and X is H or OH.

14. Use according to claim 6 or 13 in the manufacture of a medicament for the prevention, treatment, or amelioration of pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncope, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina,

exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterans), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

15. Use of a compound of claim 1 or 2, compound 13 or a pharmaceutically acceptable salt of compound 13, or a compound of formula (V) as defined in claim 13 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prevention, treatment, or amelioration of macro or micro vascular complications of type 1 and 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis.

16. Use of a compound of claim 1 or 2, or a pharmaceutically acceptable salt of a compound of formula (V) as defined in claim 13, for the manufacture of a medicament for the prevention, treatment, or amelioration of inflammation.

17. Use according to claim 16 for the prevention, treatment, or amelioration of inflammation caused by or associated with: cancer (such as leukemias, lymphomas, carcinomas, colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and prostate metastases, etc.); auto-immune disease (such as organ transplant rejection, lupus erythematosus, graft v. host rejection, allograft rejections, multiple sclerosis, rheumatoid arthritis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes); autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis); obesity; cardiovascular conditions associated with poor tissue perfusion and inflammation (such as atheromas, atherosclerosis, stroke, ischaemia-reperfusion injury, claudication, congestive heart failure, vasculitis, haemorrhagic shock, vasospasm following subarachnoid haemorrhage, vasospasm following cerebrovascular accident, pleuritis, pericarditis, the cardiovascular complications of diabetes); ischaemia-reperfusion injury, ischaemia and associated inflammation, restenosis following angioplasty and inflammatory aneurysms; epilepsy,

neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), fibrosis (for example of the lung, skin and liver), sepsis, septic shock, encephalitis, infectious arthritis, Jarisch-Herxheimer reaction, shingles, toxic shock, cerebral malaria, Lyme's disease, endotoxic shock, gram negative shock, haemorrhagic shock, hepatitis (arising both from tissue damage or viral infection), deep vein thrombosis, gout; conditions associated with breathing difficulties (e.g. chronic obstructive pulmonary disease, impeded and obstructed airways, bronchoconstriction, pulmonary vasoconstriction, impeded respiration, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, bronchial allergy and/or inflammation, asthma, hay fever, rhinitis, vernal conjunctivitis and adult respiratory distress syndrome); conditions associated with inflammation of the skin (including psoriasis, eczema, ulcers, contact dermatitis); conditions associated with inflammation of the bowel (including Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, inflammatory bowel disease); HIV (particularly HIV infection), bacterial meningitis, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, osteoporosis and other bone resorption diseases, osteoarthritis, rheumatoid arthritis, infertility from endometriosis, fever and myalgia due to infection, cachexia secondary to cancer, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment, and other conditions mediated by excessive anti-inflammatory cell (including neutrophil, eosinophil, macrophage and T- cell) activity.

18. Use of a compound of formula 1 or 2, compound 13 or a pharmaceutically acceptable salt of compound 13, or a compound of formula (V) as defined in claim 13 or a pharmaceutically acceptable salt thereof, in the manufacture of a disease-modifying antirheumatic drug (DMARD) for slowing the progression of arthropathy.

19. Use according to claim 18 in the manufacture of a DMARD for slowing the progression of rheumatoid arthritis.
20. Use according to any of claims 3 to 19 at a dosage which, after administration to a subject, gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.
21. Use according to any of claims 3 to 20 at a dosage that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.
22. Use according to claim 21, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects.
23. Use according to any of claims 3 to 22 at a dosage which, after administration to a subject, gives rise to a plasma concentration of the compound that is maintained for more than one hour between one thousandth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.
24. Use according to any of claims 3 to 23 at a dosage of less than 6mg/kg.
25. Use according to any of claims 3 to 24 at a dosage of at least 0.01mg/kg.
26. Use according to any of claims 3 to 25 at a dosage of 0.2 to 1mg/kg.
27. A method of preventing, treating, or ameliorating a pathological condition that can be prevented or improved by agonism of adenosine A2A receptors, which comprises administering a compound according to claim 1 or 2, or a pharmaceutically acceptable salt of a compound of formula (V) as defined in claim 13, to a subject in need of such prevention, treatment, or amelioration.

28. A method of preventing, treating, or ameliorating a pathological condition that can be prevented or improved by agonism of adenosine A2A receptors, excluding pain, cancer, inflammation, auto-immune disease, ischemia-reperfusion injury, epilepsy, sepsis, septic shock, neurodegeneration (including Alzheimer's Disease), muscle fatigue and muscle cramp, which comprises administering a compound of formula (V) as defined in claim 13 to a subject in need of such prevention, treatment, or amelioration.

29. A method of preventing, treating, or ameliorating pain which comprises administering a compound according to claim 1 or 2, or compound 13 or a pharmaceutically acceptable salt of compound 13, or a pharmaceutically acceptable salt of a compound of formula (V) as defined in claim 13, to a subject in need of such prevention, treatment, or amelioration.

30. A method of preventing, treating, or ameliorating ischaemic pain which comprises administering a compound according to claim 1 or 2, compound 13 or a pharmaceutically acceptable salt of compound 13, or a compound of formula (V) as defined in claim 13 or a pharmaceutically acceptable salt thereof, to a subject in need of such prevention, treatment, or amelioration.

31. A method according to claim 30 for the prevention, treatment, or amelioration of ischaemic pain associated with coronary artery disease, peripheral artery disease, left ventricular hypertrophy, essential hypertension, acute hypertensive emergency, cardiomyopathy, heart insufficiency, exercise tolerance, chronic heart failure, arrhythmia, cardiac dysrhythmia, syncope, arteriosclerosis, mild chronic heart failure, angina pectoris, Prinzmetal's (variant) angina, stable angina, exercise induced angina, cardiac bypass reocclusion, intermittent claudication (arteriosclerosis obliterans), arteritis, diastolic dysfunction, systolic dysfunction, atherosclerosis, post ischaemia/reperfusion injury, diabetes (Types I or II), thromboembolisms, haemorrhagic accidents, or neuropathic or inflammatory pain arising from hypoxia-induced nerve cell damage.

32. A method of prevention, treatment, or amelioration of inflammation, which comprises administering a compound as defined in claim 1 or 2, or a pharmaceutically acceptable salt of a compound of formula (V) as defined in claim 13, to a subject in need of such prevention, treatment, or amelioration.

33. A method according to claim 32 for the prevention, treatment, or amelioration of inflammation caused by or associated with: cancer (such as leukemias, lymphomas, carcinomas, colon cancer, breast cancer, lung cancer, pancreatic cancer, hepatocellular carcinoma, kidney cancer, melanoma, hepatic, lung, breast, and prostate metastases, etc.); auto-immune disease (such as organ transplant rejection, lupus erythematosus, graft v. host rejection, allograft rejections, multiple sclerosis, rheumatoid arthritis, type I diabetes mellitus including the destruction of pancreatic islets leading to diabetes and the inflammatory consequences of diabetes); autoimmune damage (including multiple sclerosis, Guillam Barre Syndrome, myasthenia gravis); obesity; cardiovascular conditions associated with poor tissue perfusion and inflammation (such as atheromas, atherosclerosis, stroke, ischaemia-reperfusion injury, claudication, congestive heart failure, vasculitis, haemorrhagic shock, vasospasm following subarachnoid haemorrhage, vasospasm following cerebrovascular accident, pleuritis, pericarditis, the cardiovascular complications of diabetes); ischaemia-reperfusion injury, ischaemia and associated inflammation, restenosis following angioplasty and inflammatory aneurysms; epilepsy, neurodegeneration (including Alzheimer's Disease), muscle fatigue or muscle cramp (particularly athletes' cramp), arthritis (such as rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis), fibrosis (for example of the lung, skin and liver), sepsis, septic shock, encephalitis, infectious arthritis, Jarisch-Herxheimer reaction, shingles, toxic shock, cerebral malaria, Lyme's disease, endotoxic shock, gram negative shock, haemorrhagic shock, hepatitis (arising both from tissue damage or viral infection), deep vein thrombosis, gout; conditions associated with breathing difficulties (e.g. chronic obstructive pulmonary disease, impeded and obstructed airways, bronchoconstriction, pulmonary vasoconstriction, impeded respiration, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcosis, cystic fibrosis, pulmonary hypertension, pulmonary vasoconstriction, emphysema, bronchial allergy and/or inflammation, asthma, hay fever, rhinitis, vernal conjunctivitis and

adult respiratory distress syndrome); conditions associated with inflammation of the skin (including psoriasis, eczema, ulcers, contact dermatitis); conditions associated with inflammation of the bowel (including Crohn's disease, ulcerative colitis and pyresis, irritable bowel syndrome, inflammatory bowel disease); HIV (particularly HIV infection), bacterial meningitis, TNF-enhanced HIV replication, TNF inhibition of AZT and DDI activity, osteoporosis and other bone resorption diseases, osteoarthritis, rheumatoid arthritis, infertility from endometriosis, fever and myalgia due to infection, cachexia secondary to cancer, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS related complex (ARC), keloid formation, scar tissue formation, adverse effects from amphotericin B treatment, adverse effects from interleukin-2 treatment, adverse effects from OKT3 treatment, or adverse effects from GM-CSF treatment, and other conditions mediated by excessive anti-inflammatory cell (including neutrophil, eosinophil, macrophage and T- cell) activity.

34. A method of preventing, treating, or ameliorating macro or micro vascular complications of type 1 and 2 diabetes, retinopathy, nephropathy, autonomic neuropathy, or blood vessel damage caused by ischaemia or atherosclerosis which comprises administering a compound of claim 1 or 2, compound 13 or a pharmaceutically acceptable salt of compound 13, or a compound of formula (V) as defined in claim 13 or a pharmaceutically acceptable salt thereof, to a subject in need of such prevention, treatment, or amelioration.

35. A method of slowing the progression of arthropathy, which comprises administering a compound of formula 1 or 2, compound 13 or a pharmaceutically acceptable salt of compound 13, or a compound of formula (V) as defined in claim 13 or a pharmaceutically acceptable salt thereof, as a disease-modifying antirheumatic drug (DMARD) to a subject in need thereof.

36. A method according to claim 35, for slowing the progression of rheumatoid arthritis.

37. A method according to any of claims 27 to 36, wherein the compound is administered at a dose that gives rise to a peak plasma concentration of the compound that is less than the EC50 value of the compound at adenosine receptors at pH 7.4.
38. A method according to any of claims 27 to 37, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.
39. A method according to any of claims 27 to 38, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest EC50 value of the compound at adenosine receptors.
40. A method according to any of claims 27 to 39, wherein the compound is administered to the subject in an amount that results in a peak plasma concentration of the compound in the subject that is one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.
41. A method according to any of claims 27 to 40, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the lowest Kd value of the compound at adenosine receptors.
42. A method according to any of claims 27 to 41, wherein the compound is administered to the subject in an amount that is one ten thousandth to one fifth of the minimum amount of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.

43. A method according to any of claims 27 to 42, wherein the compound is administered at a dose that is one thousandth to one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the dose is to be administered.
44. A method according to claim 43, wherein the dose is one hundredth to one fifth of the minimum dose that gives rise to the side effects
45. A method according to any of claims 27 to 44, wherein the compound is administered to the subject in an amount that results in a plasma concentration of the compound in the subject being maintained for more than one hour at one ten thousandth to one fifth of the minimum plasma concentration of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is administered.
46. A method according to any of claims 27 to 45, wherein the compound is administered at a dose that results in a plasma concentration of the compound that is maintained for more than one hour between one hundredth and one fifth of the minimum dose of the compound that gives rise to bradycardia, hypotension or tachycardia side effects in animals of the same species as the subject to which the compound is to be administered.
47. A method according to any of claims 27 to 46, wherein the compound is administered at a dose of less than 6mg/kg.
48. A method according to any of claims 27 to 47, wherein the compound is administered at a dosage of 0.001 to 6 mg/kg.
49. A method according to any of claims 27 to 48, wherein the compound is administered at a dose of at least 0.01mg/kg.
50. A method according to any of claims 27 to 49, wherein the compound is administered at a dose of 0.2 to 1mg/kg.

51. A method according to any of claims 27 to 50, wherein the compound is administered orally, parenterally, sublingually, transdermally, intrathecally, transmucosally, intravenously, intramuscularly, subcutaneously, topically, or by inhaling.

52. A method according to any of claims 27 to 51, wherein the compound is administered at a frequency of 2 or 3 times per day.

53. A method according to any of claims 27 to 52, wherein the subject is a human subject.

54. Use according to claim 18 or 19, or a method according to claim 35 or 36, wherein the compound is spongiosine or a pharmaceutically acceptable salt thereof.

55. A pharmaceutical composition in unit dose form comprising up to 500mg of a compound as defined in claim 1 or 2, and a physiologically acceptable carrier, excipient, or diluent.

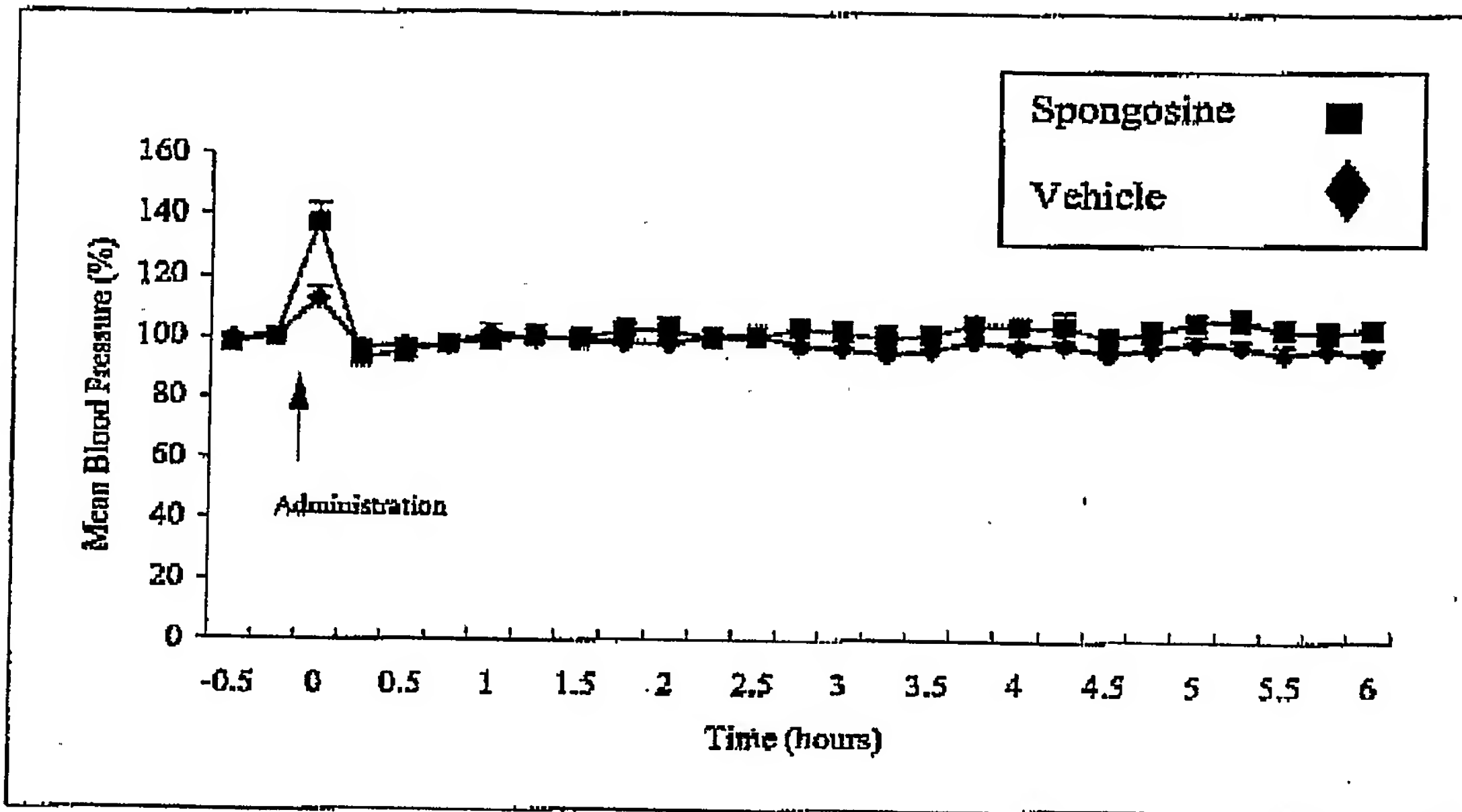
56. A pharmaceutical composition in unit dose form comprising upto 500mg of a compound as defined in claim 1 or 2, or compound 13 or a pharmaceutically acceptable salt of compound 13, or a compound of formula (V) as defined in claim 13 or a pharmaceutically acceptable salt thereof, together with an NSAID or a DMARD, and a physiologically acceptable carrier, excipient, or diluent.



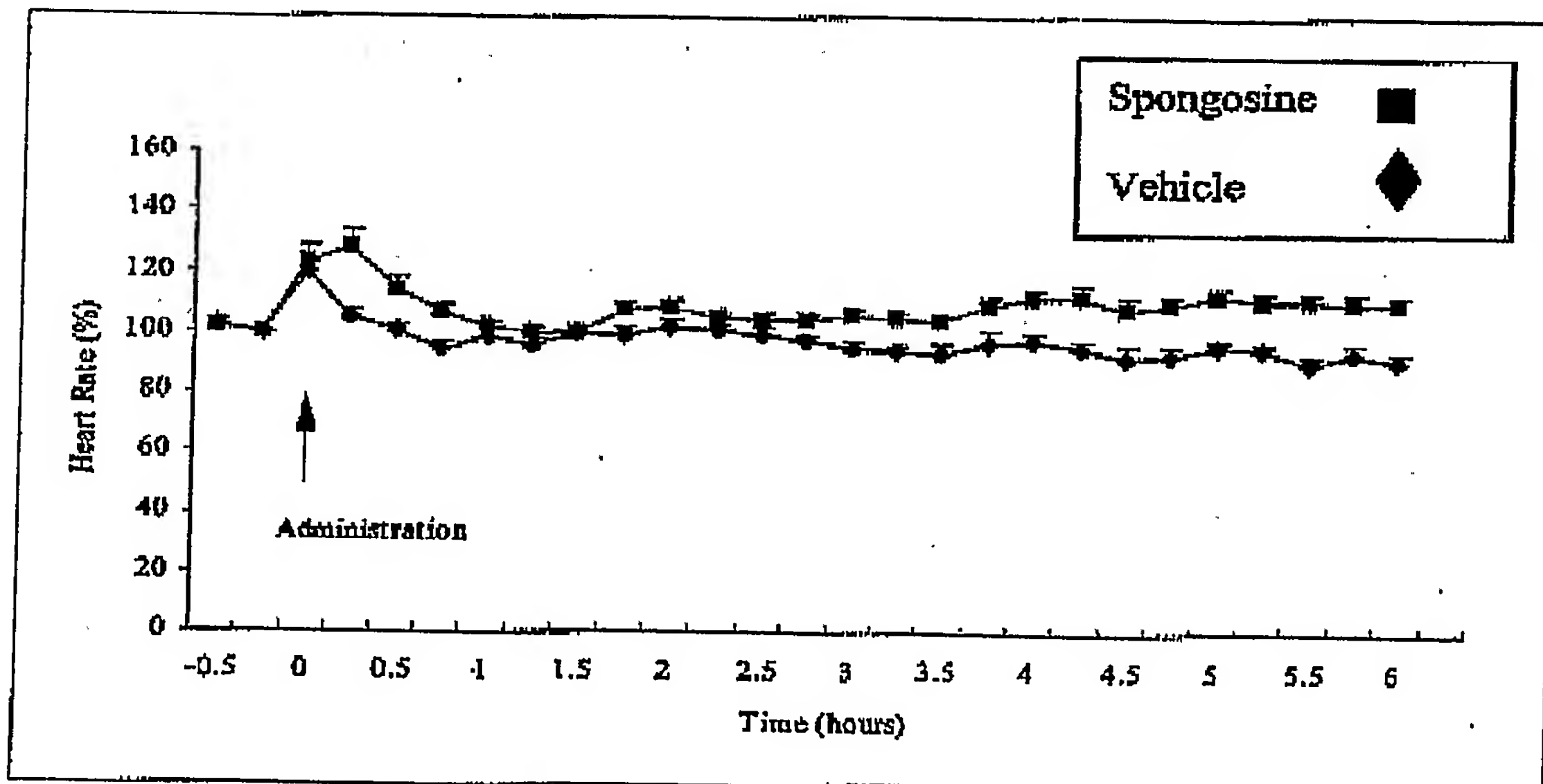
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Figure 1

A)

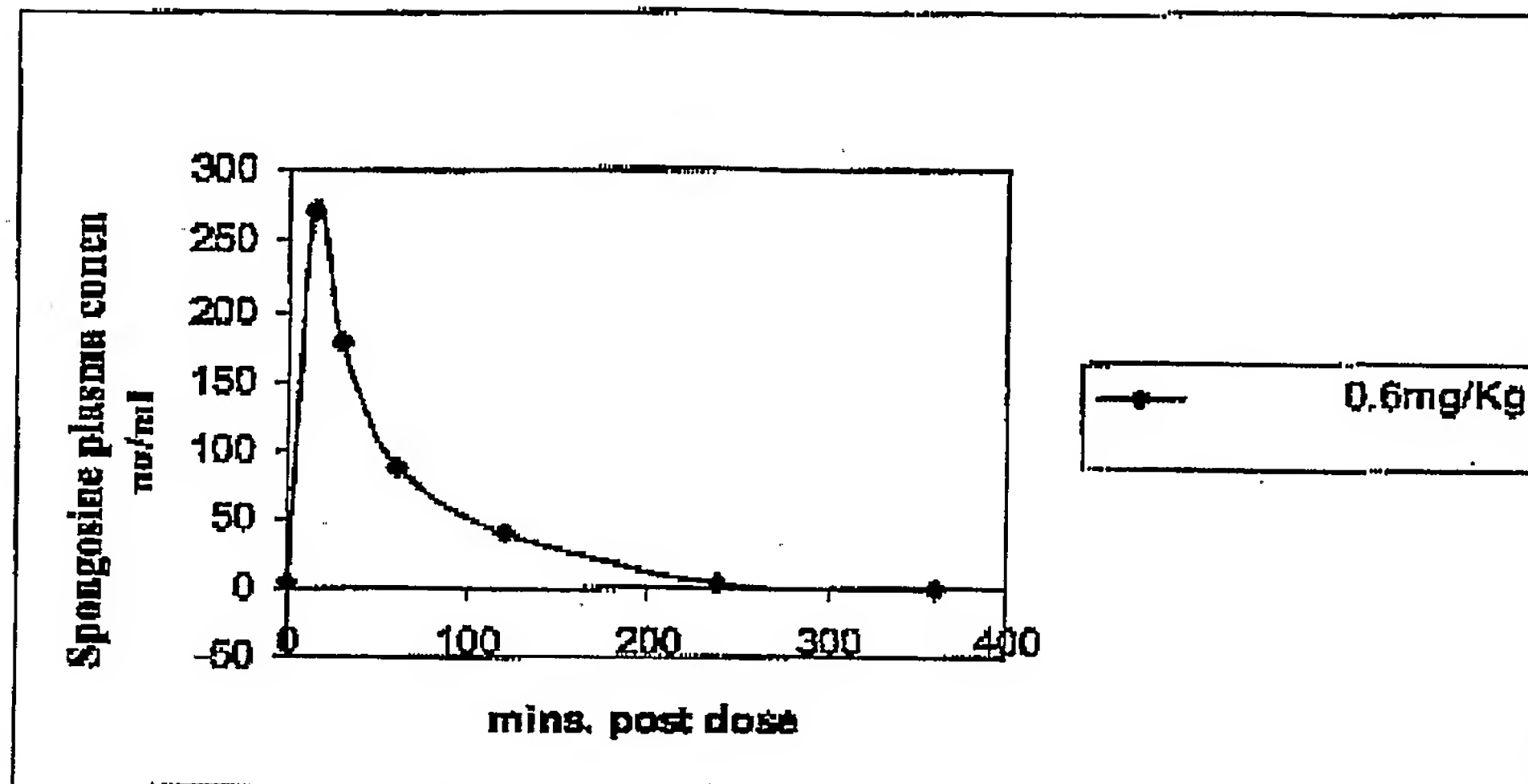


B)





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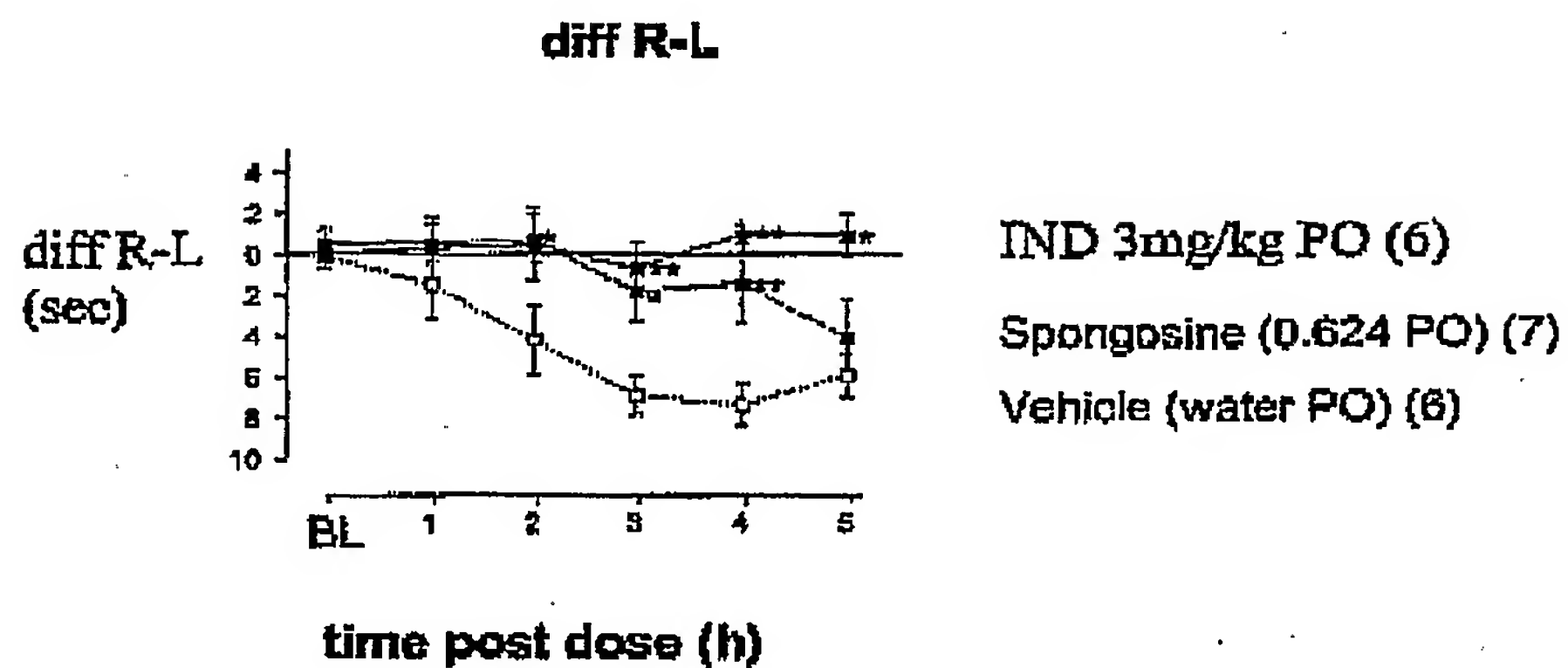
Figure 2



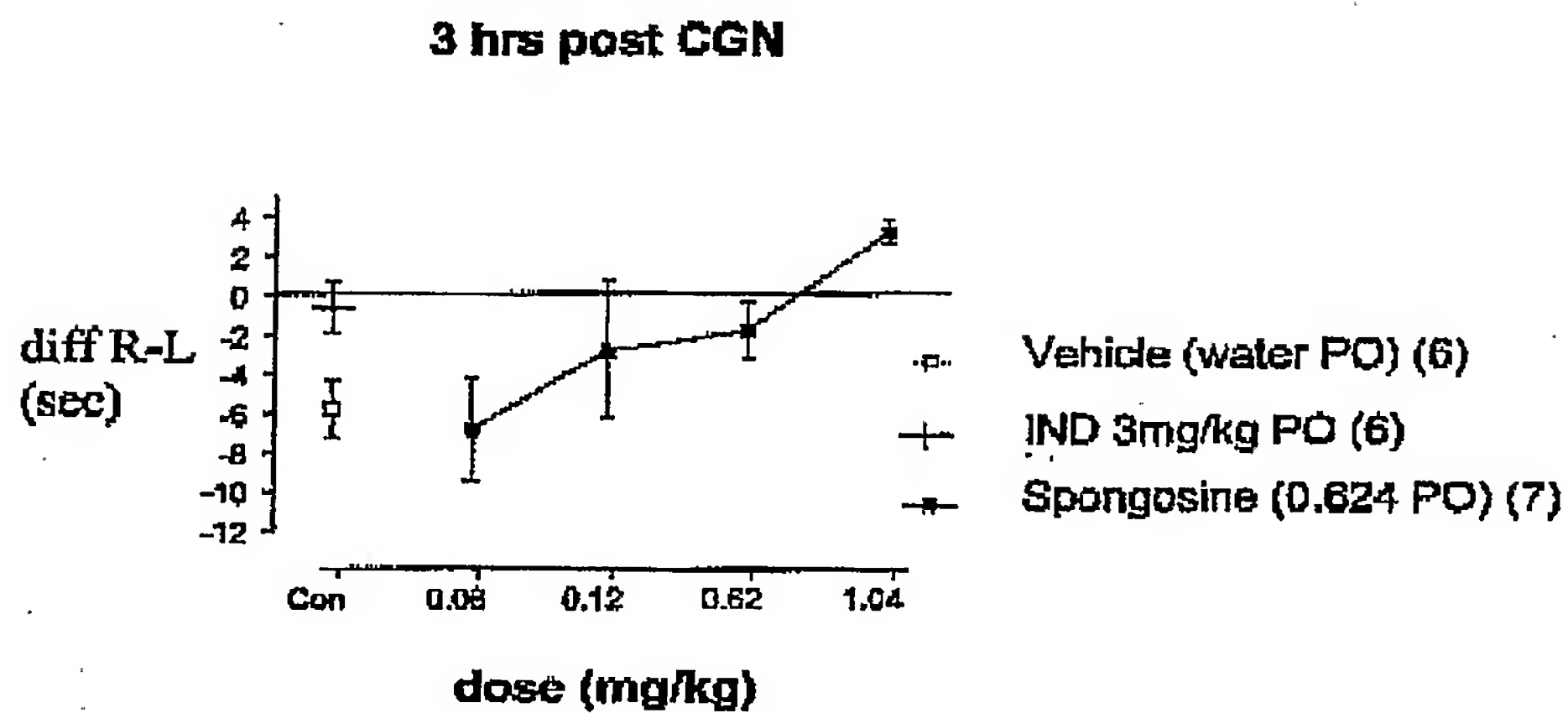
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Figure 3

A)



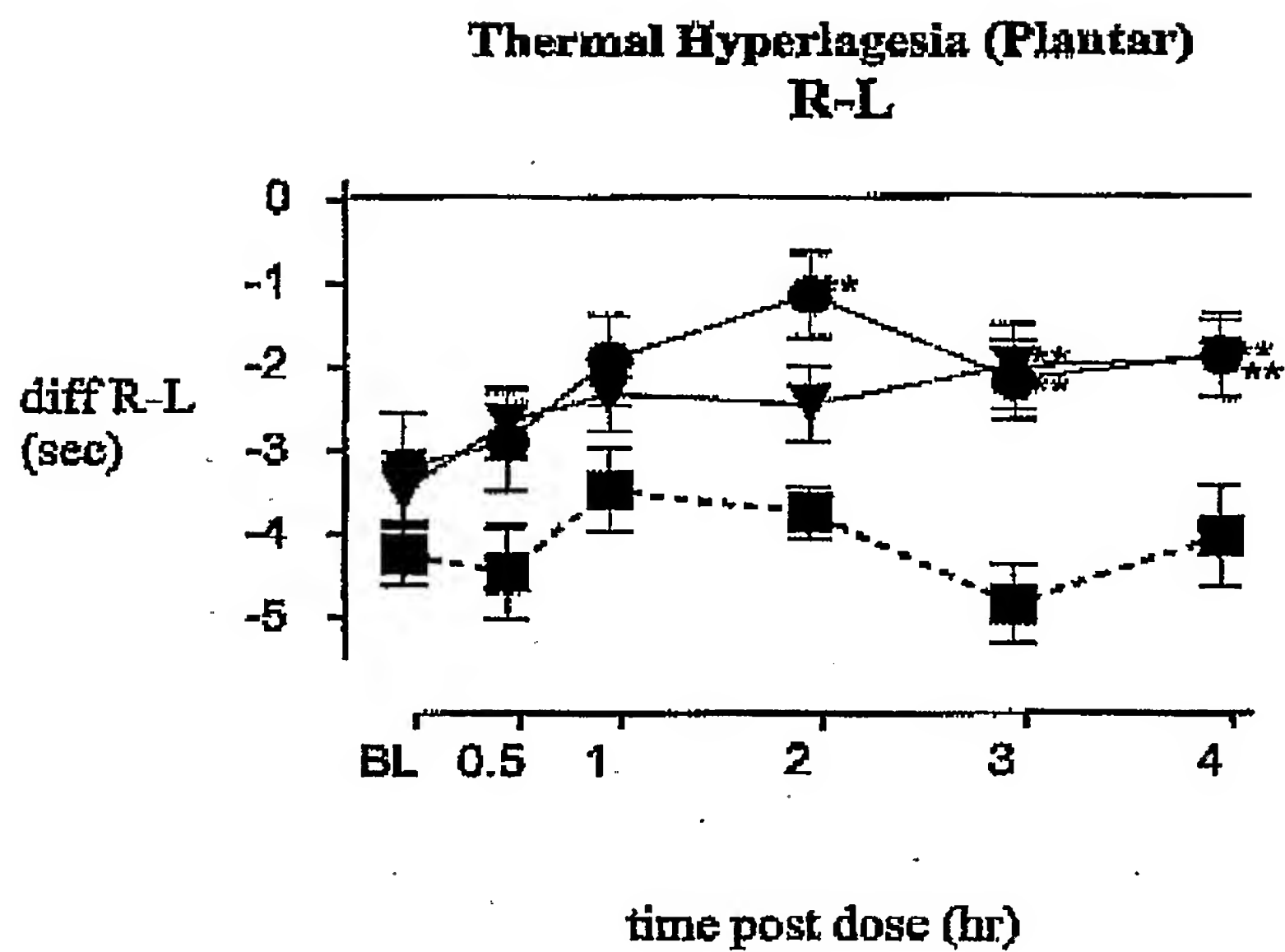
B)





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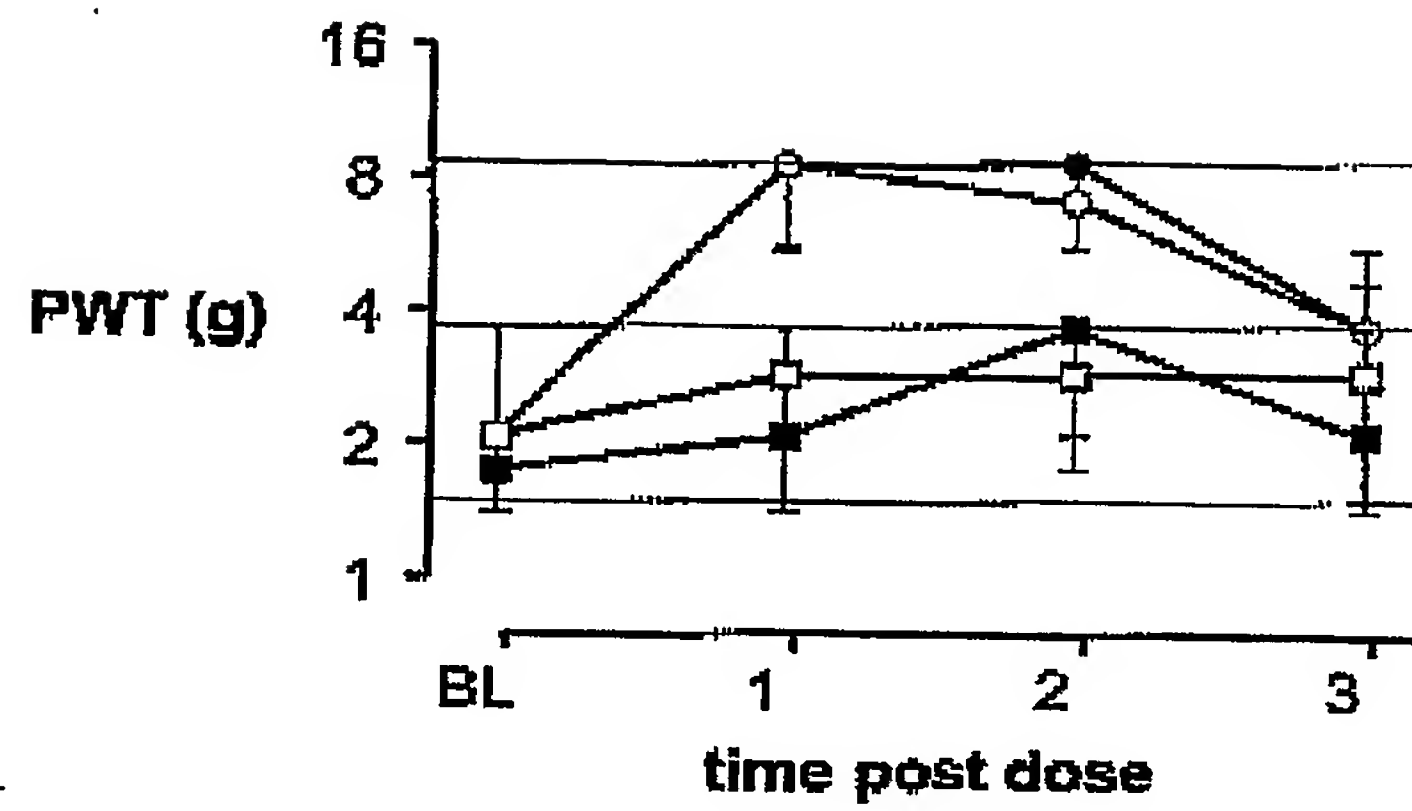
Figure 4





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Figure 5



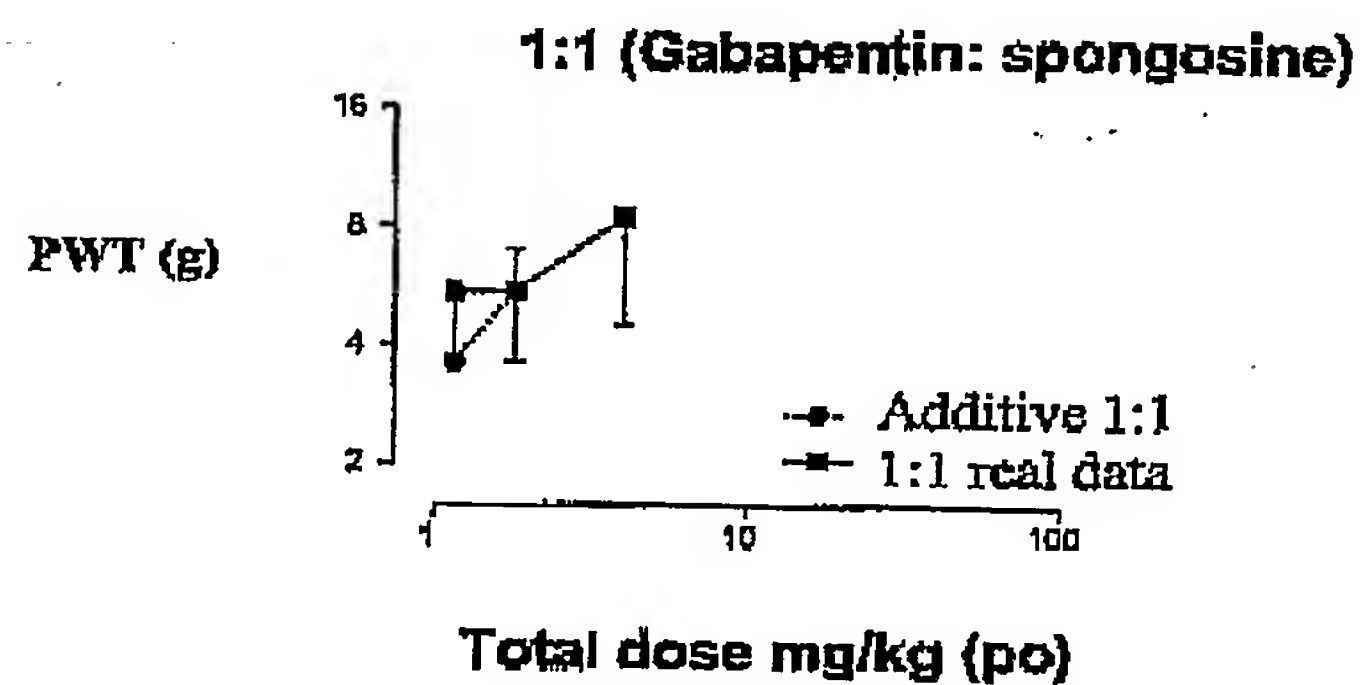
- Vehicle + Vehicle
- Vehicle + spongostin (1.2 p.o.)
- Nalox (1 s.c.) + Vehicle
- Nalox (1 s.c.) + spongostin (1.2 p.o.)



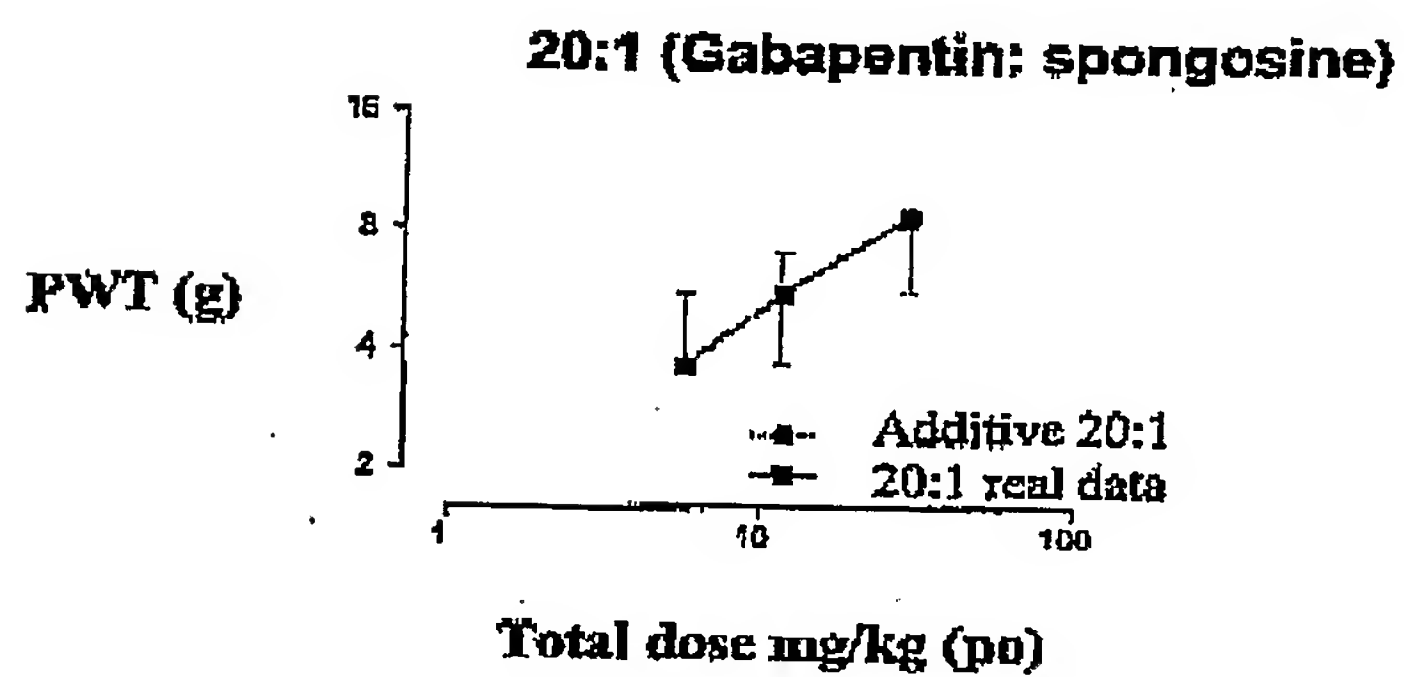
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Figure 6

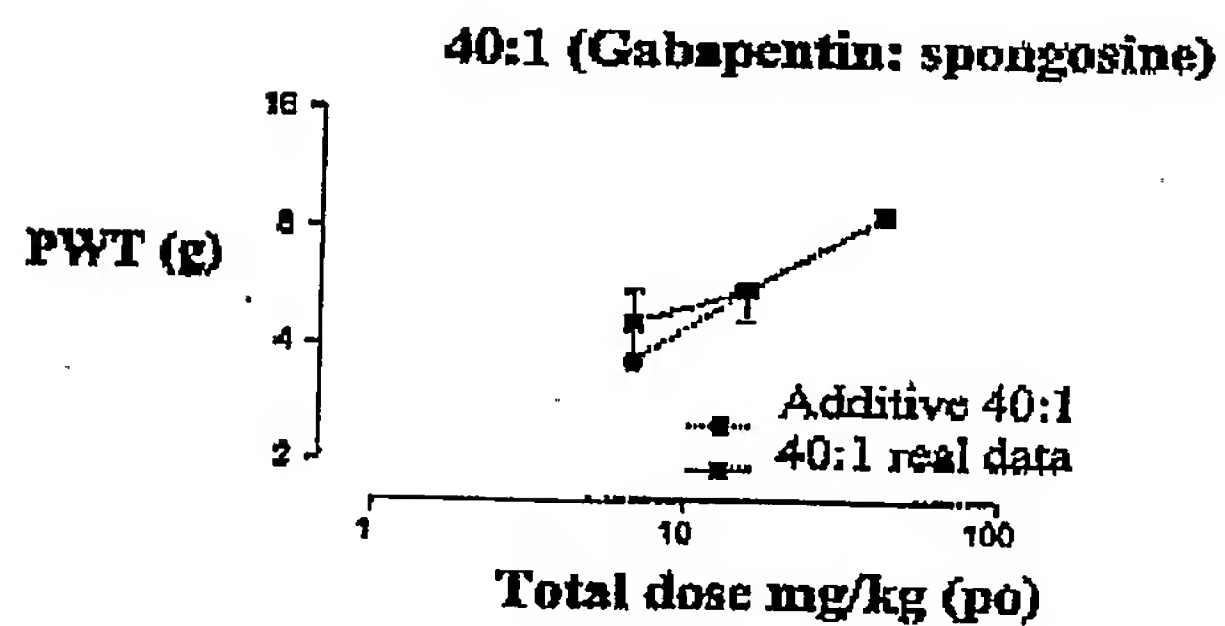
A)



B)



C)





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Figure 7

Effect of Spongosine on LPS-stimulated TNF alpha release

